Journal of Food and Nutrition Sciences
2026, Vol. 14, No. 4, pp. 250–257
https://doi.org/10.11648/j.jfns.20261404.14

Research Article

The Truffle (T. Magnatum) Mycelium Modulates Homeostasis Regulators: An Open Human Study

Tetsuya Konishi[1, *], Rakan Matsui[2], Kennichi Watanabe[3], Ken Usami[4], Akinori Iguchi[1], Saori Nakagawa[5]

[1]Faculty of Applied Life Sciences, Niigata University of Pharmacy and Medical and Life Sciences, Niigata, Japan
[2]Risaraopt Co. Ltd, Osaka, Japan
[3]Faculty of Medicine, Niigata University, Niigata, Japan
[4]Niigata Beer Co. Ltd, Niigata, Japan
[5]Department of Clinical Engineering and Medical Technology, Niigata University of Health and Welfare, Niigata, Japan

Abstract

Based on our previous observation that the truffle (T. magnatum) mycelium extract enhanced DHEA in rats, the anti-metabolic disorder function of the extract was investigated in a cohort of 20 volunteers without chronic diseases (mean age: 54.2 ± 5.4 years; baseline HbA1c: 5.3-6.3%), including 12 men (53.8 ± 6.2 years) and 8 women (54.6 ± 4.5 years). They consumed one gel pack containing artificially cultivated truffle mycelium extract (equivalent to 2.8 g of truffle mycelium) approximately 30 minutes before breakfast and dinner for 12 weeks. In addition to general health indicators, selected biomarkers related to metabolic regulation and disorders were measured before and after the intervention. Although markers of metabolic syndrome, such as plasma triglycerides and LDL cholesterol levels, did not show meaningful changes after the intervention, significant increases ($p < 0.05$) in endocrine factors, including DHEA, 1,25-dihydroxyvitamin D3, adiponectin, and insulin, as well as NK cell activity, were observed. Some markers of liver and kidney damage, such as the A/G ratio and creatinine, improved significantly after truffle intake, as did erythrocyte condition. In addition, gender differences were notable in several markers, especially endocrine factors and liver function. To further evaluate its effects, participants were stratified by baseline HbA1c into a higher group (≥ 5.9%, mean 6.0 ± 0.116%, n = 8) and a lower group (< 5.8%, mean 5.5 ± 0.159%, n = 12). The two groups showed contrasting responses: in the higher HbA1c group, several metabolic syndrome markers tended to decrease (negative net changes), whereas in the lower HbA1c group, changes remained modestly positive after the truffle intake period. However, the differences between the two groups did not reach statistical significance for most markers. Notably, liver damage markers AST and ALT differed significantly between the two groups, indicating that liver-protective function is more pronounced in a metabolically distorted state. These results indicate that truffle extract does not directly improve the distorted metabolic condition but may do so indirectly by inducing homeostasis regulators.

Keywords

Truffle Magnatium, Metabolic Syndrome, Mibyou-care, Homeostasis Regulator, DHEA

*Correspondence: Tetsuya Konishi (t.konishi@bg.wakwak.com), Tetsuya Konishi (konishi@nupals.ac.jp)

Received: 3 July 2026; **Accepted:** 20 July 2026; **Published:** 10 August 2026

1. Introduction

The global increase in diabetes, particularly type 2 diabetes, has emerged as a critical social issue that threatens health and well-being in aging societies [1]. Type 2 diabetes is a major causative risk factor for fatal diseases such as cardiovascular disease [2], stroke [3], certain cancers [4], and dementia [5]. This condition is characterized by chronic hyperglycemia resulting from insulin resistance [6]. The primary pathogenic factors of type 2 diabetes are lifestyle-related metabolic disorders, including obesity, hyperlipidemia, and hypertension [7]. Currently, several clinical medicines, such as metformin [8, 9] and GLP-1 agonists [10-12], are used to treat obesity and metabolic syndrome. However, preventive approaches are also critical for controlling metabolic disorders, especially in the early stages of disease development [13]. In this context, the concept of Mibyou —an asymptomatic stage of disorders characterized by subtle imbalances in metabolic homeostasis—is recognized as a primary target for intervention to prevent progression to life-threatening conditions [14-16]. Although the idea was originally described in Traditional Chinese Medicine about 2500 years ago, it was recently renovated by the Japan Mibyou Association as modern Mibyou, which includes even early stages of diseases such as metabolic syndromes [17, 18]. Therefore, Mibyou care is primarily important in preventive medicine, disease prevention, and management.

Diet and exercise are considered first-line approaches for managing metabolic syndrome, a common metabolic disorder, as noted by Mibyou [18, 19]. Recently, so-called “superfoods” have attracted increasing attention [20]. Incorporating such foods into daily diets may reduce the risk of metabolic disorders and their endpoints, including cardiovascular disease [21] and Alzheimer’s disease [22]. In addition to regular meals, dietary supplements and functional foods are also being explored as alternative strategies for the prevention and amelioration of metabolic syndrome [23-25]. Several traditionally known plant resources, such as Morus species [26], have demonstrated anti-metabolic and/or anti-diabetic effects, and extensive studies have been conducted to identify novel natural resources and their active components [27, 28].

Mushrooms and other fungi are promising natural resources due to their wide range of physiological activities, including anti-metabolic and anti-aging effects [29-31]. They are rich in nutrients, especially micronutrients, as well as non-nutritional bioactive components such as dietary fiber, terpenoids, and steroids [32]. Consequently, fungi are not only regarded as low-calorie, nutrient-rich superfoods but also as valuable sources for functional foods and medicines [33].

Truffles (Tuber spp.), members of the class Ascomycota, are highly valued culinary ingredients known for their distinctive aroma and legendary properties, including an aphrodisiac effect [34] and anti-aging properties [31, 35]. Although some studies have reported the physiological functions of black truffle (T. melanosporum), such as anti-diabetic and antioxidant activities [36, 37], functional studies on truffles remain limited, particularly for the most prized species, the white truffle (T. magnatum). This scarcity is likely due to the difficulty of obtaining sufficient quantities of material for experimental studies.

With the recent availability of artificially cultivated T. magnatum mycelium, we previously investigated the effects of aqueous ethanol extracts of cultured T. magnatum mycelium in mice and found that oral administration of the extract increased plasma levels of dehydroepiandrosterone (DHEA) [38]. Plasma DHEA levels decline with age and are implicated as a physiological anti-aging factor that functions as an endocrine regulator of metabolic homeostasis, with relevance to multiple disorders, including metabolic syndrome [39, 40] and dementia [41]. These findings suggest that T. magnatum mycelium extract may possess preventive or ameliorative potential against metabolic disorders.

In the present study, we evaluated the effects of T. magnatum mycelium extract in human volunteers over a 12-week intake period. The results indicate that T. magnatum extract may modulate key homeostatic regulators, thereby ameliorating metabolic dysfunction and helping control metabolic disorders in metabolically imbalanced conditions.

2. Materials and Methods

2.1. Participant Selection

From the 60 initial candidates registered with the clinical trial volunteer association (FeileB Co., Ltd.) and who provided informed consent after being informed of the study purpose and procedures, 20 participants were ultimately selected. Final enrollment was determined by a medical doctor based on both inclusion and exclusion criteria.

2.2. Inclusion Criteria

Age between 30 and 65 years.

BMI between 18.5 and 29.0 kg/m^2.

Participants received a full explanation of the study and provided written informed consent.

2.3. Exclusion Criteria

1) Individuals with liver dysfunction, renal disorders, cardiovascular disease, diabetes, dyslipidemia, hypertension, sleep disorders, epilepsy, or other chronic diseases, as well as a history of major gastrointestinal surgery (e.g., gastroduodenal ulcer, irritable bowel syndrome, gastrectomy, gastroenterostomy, intestinal resection).
2) Individuals taking supplements or health foods that may affect the biomarkers measured in this study.
3) Individuals whose average daily alcohol consumption

exceeded 60 g/day.
4) Individuals with extremely irregular dietary habits.
5) Individuals who are likely to change their lifestyle patterns during the study period.
6) Individuals receiving medications such as drugs for intestinal disorders, Kampo medicine, or over-the-counter remedies.
7) Individuals with chronic atopic dermatitis or other allergic conditions.
8) Individuals with a history of anaphylactic shock.
9) Individuals judged unsuitable as study participants by the principal medical doctor.

2.4. Trial Schedule

At baseline (Visit 0), initial physical and clinical assessments were performed, including height, body weight, BMI, body composition, blood pressure, pulse, routine and selected blood markers, urine markers, and an oral glucose tolerance test (OGTT). Following screening, 20 participants were enrolled and instructed to consume one gel packet containing truffle mycelium extract (2.8 g as Truffle mycelium) approximately 30 minutes before breakfast and dinner (2 packs per day) for 12 weeks from day 1 (Visit 1) to day 94 (Visit 2). At the end of the intervention (Visit 2), the same biological and clinical assessments were repeated. The biomarkers analyzed are listed below, and the results are summarized in Supplementary Table 1. Adverse events related to truffle gel intake were also monitored throughout the trial. The test gel pack sample of truffle mycelium extract is the same as a commercially available product, and the dose was determined based on a previous animal experiment [38].

2.4.1. Routine Blood Markers

White blood cell subsets (eosinophils, basophils, neutrophils), erythrocytes, MCV, MCH, MCHC, triglycerides, bilirubin, AST, ALT, LDH, γ-GT, CPK, uric acid, blood urea nitrogen, creatinine, minerals (Na, K, Cl, Ca, Zn), total protein, albumin, A/G ratio, plasma iron, CK, HbA1c, fasting blood glucose, insulin, LDL-cholesterol, HDL-cholesterol, total cholesterol, and ALP.

2.4.2. Selected Blood Markers

DHEA, testosterone, estradiol, pentcidine, cortisol, cholinesterase, somatomedin C (IGF-1), natural killer (NK) cell activity, lactic acid, ferritin, 1,25-dihydroxyvitamin D3, adiponectin, zinc, hsCRP, and sd-LDL.

2.4.3. OGTT Procedure

TRELAN G 75 (AY Pharma Co., Ltd., Japan) was administered orally, and plasma glucose was measured at 30, 60, 90, and 120 minutes post-ingestion.

2.5. Adverse Effects and Dropouts

No participants withdrew during the trial, and no observable adverse events were reported.

2.6. Data Processing and Statistical Analysis

All data are presented as mean ± standard deviation (SD), along with the distribution (minimum, median, and maximum values). To compare values before (Visit 1) and after 12 weeks (Visit 2) of the truffle intake period, statistical analyses were performed using the Wilcoxon signed-rank test, a nonparametric test in SPSS version 29 (IBM Corp.). All 20 participants completed the protocol and were included in the Full Analysis Set (FAS).

For subgroup analyses, net changes in biomarkers were also compared between participants with higher and lower baseline HbA1c using paired t-tests.

2.7. Test Sample Preparation

The gel packets (a commercially available product named Drops of Truffle) were prepared and provided by Niigata Beer Co., Ltd. The dose of truffle extract and the nutritional composition of the gel packs are provided in Supplement Data 1.

2.8. Ethics

This study was conducted in accordance with the Declaration of Helsinki (revised at the 2013 WMA General Assembly in Fortaleza) and the Ethical Guidelines for Medical and Health Research Involving Human Subjects (Ministry of Education, Culture, Sports, Science and Technology; Ministry of Health, Labour and Welfare, Japan). To ensure participants' rights, safety, and data reliability, the protocol was reviewed and approved by the Institutional Review Board for "Research Involving Human Subjects". The study was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR, registration number: UMIN000048820).

3. Results

Changes in common health check biomarkers and selected markers of cellular metabolism were measured in 20 volunteers before (Visits 0 and 1) and after the 12-week truffle mycelium intake period (Visit 2). The full dataset is presented in Supplement Data 2. The statistical significance of the changes was assessed using a nonparametric test due to the small dataset size. Markers showing significant net differences between before and after the truffle intake period in the full dataset and in the male and female groups are summarized in Table 1, with gender-specific changes analyzed separately. (Tables 1 and 2 are set in the Supplement Material Section together with Supplement Data 1 and 2, because of their data

size).

Notably, markers related to endocrine and immune function increased significantly after the truffle intake period compared with baseline (Visit 1 or V0), including DHEA ($p = 0.033$), 1,25-dihydroxy-vitamin D3 ($p < 0.001$), adiponectin ($p < 0.001$), insulin ($p = 0.019$), and NK cell activity ($p = 0.017$ at E: T = 10: 1, $p = 0.021$ at E: T = 20: 1). Testosterone, on the other hand, significantly decreased ($p = 0.048$).

Besides endocrine factors, markers of liver and kidney function, including the A/G ratio (p=0.029) and creatinine (p=0.023), showed significant decreases. In addition, several anthropometric and epidemiologic factors changed slightly but significantly, with BMI (p=0.045), HOMA-R (p=0.016), hematocrit (p=0.030), MCV (p=0.003), and plasma K level (p=0.018) showing slight increases, except for MCHC (p=0.001) (Table 1 and Supplement Data 2, in the Supplement Material section).

OGTT plasma glucose values decreased at 30, 60, 90, and 120 minutes, but the changes were not statistically significant (Supplementary Table 1).

When the effect of truffle intake was assessed separately in the male and female groups, markers such as hematocrit (p=0.025), plasma K (p=0.009), dihydroxy-vitamin D3 (p <0.001), somatomedin C (p=0.021), estradiol (p=0.037), γ-GT (p=0.037), and choline esterase (p=0.037) showed statistically significant increases in the male group after the truffle intake period. In contrast, decreases in testosterone (p=0.023) and A/G (p=0.048) were significant in the female group, indicating that truffle mycellium has gender-specific effects. Obvious differences in the net change in marker levels after the truffle intake period were noted between the sexes, with somatomedin C (13.0 for male vs -7.0 for female), testosterone (-64.1 for male vs -4.3 for female), estradiol (-4.2 for male vs 10.9 for female), γ-GT (7.33 for male vs -2.0 for female), and choline esterase (13.2 for male vs 6.0 for female) (Table 1).

To further evaluate the effects of truffle supplementation on metabolic disorders, participants were divided into higher- and lower-HbA1c groups based on baseline HbA1c (the average of Visits 0 and 1). Using the diagnostic criteria for prediabetes (5.7-6.5%) [42, 43] and the HbA1c distribution in this study (5.3-6.2%, mean 5.7%), a cutoff of 5.9% was used. Twelve participants were classified as the lower-HbA1c group (<5.8%, mean 5.5 ± 0.159%; 8 males, 5 females), and eight as the higher-HbA1c group (⩾5.9%, mean 6.0 ± 0.116%; 4 males, 3 females). After 12 weeks of the truffle intake period, net changes in marker levels were compared between the higher- and lower-HbA1c groups. A few markers showed statistically significant group differences after the intake period, including liver damage markers (AST, p=0.029, and ALT, p=0.026) and NK cell activity (p=0.007 for NK: E/T=10/1 (%) and p=0.016 for 20/1 (%), respectively), but all other markers showed p-values greater than 0.05. However, notable differences in the trends of net changes from the initial stage (V2-V1) were observed in marker levels associated with metabolic disorders between the higher- and lower-HbA1c groups (Table 2).

Marker levels, including BMI, body weight, body fat, total cholesterol, triglycerides, fasting plasma glucose, sd-LDL, AUC (V0/V1), and HbA1c, showed negative values, that is, the net changes decreased in the higher HbA1c group but not in the lower group. The same trend was observed in liver damage markers. Endocrine markers did not show significant differences between the groups, but NK activity was significantly lower in the higher HbA1c group than in the lower group (p=0.011 and p=0.017, respectively). These trends in marker changes were the same when the cutoff was set at 6.0%, but such group differences were not obvious when the cutoff was set at 5.7% (data not shown).

BMI is another diagnostic criterion for metabolic disorder [43]. Therefore, participants with BMI ≥ 25 kg/m^2 (n = 9; 2 males, 7 females) were analyzed separately. No significant changes were observed in this subgroup after 12 weeks of truffle intake, although several markers showed negative net changes from baseline levels, including iron, ferritin, A/G ratio, estradiol, testosterone, ALP/LFC, and creatinine (data not shown).

4. Discussion

The present study involving 20 adult volunteers revealed that intake of an aqueous ethanol extract of artificially cultured T. magnatum mycelium significantly increased plasma levels of endocrine factors, including DHEA, 1,25-dihydroxy-vitamin D3, adiponectin, and insulin, as well as the immune factor, NK cell activity. At the same time, biomarkers associated with liver and kidney function showed trends toward normalization, although statistical significance was observed only for A/G and creatinine (Table 1 and Supplement Data 2).

A gender-specific effect of truffle was also observed, particularly in endocrine factors. For example, Somatomedin C increased in males but decreased in females. Testosterone decreased in both sexes, but the decrease was more pronounced in males. In contrast, estradiol decreased in males but increased in females. However, other endocrine components, including DHEA, did not show notable gender differences. In addition, the liver damage marker, typically γ-GT, decreased in the female group but increased, not significantly, in the male group.

HbA1c is widely used as a diagnostic criterion for diabetes, and the range of 5.7-6.5% is used to define prediabetes. However, HbA1c alone may fail to identify all individuals at high risk and thus requires consideration alongside other indices, such as fasting blood glucose [42, 43]. The effect of truffle mycelium was further analyzed in a subgroup stratified by baseline HbA1c (cutoff 5.9%). Interesting trends in net changes in markers after the truffle intake period were observed across the subgroups. Although most markers did not reach statistical significance for between-group differences, except for liver function

and immune cell markers, markers related to metabolic disorders showed contrasting trends between the subgroups. Body weight, BMI, fat mass, triglycerides, total cholesterol, somatomedin C, LDL cholesterol, and sd-LDL tended to decrease after truffle intake in the higher HbA1c group (⩾5.9%, mean 6.0 ± 0.116%, n = 8), resulting in negative values, but they remained positive in the lower HbA1c group (<5.8%, mean 5.5 ± 0.159%, n = 12). (Table 2).

Liver damage markers, typically AST and ALT, decreased in the higher HbA1c group, indicating an ameliorative effect of truffle mycelium under metabolically distorted conditions. However, the effect of truffle on immune cell activation was weak under that condition (Table 2).

Further study is needed in individuals with higher baseline HbA1c, which predicts prediabetes and diabetes, to determine whether truffle mycelium can normalize the metabolically impaired state indicated by HbA1c. Overall, the pattern supports the hypothesis that truffle intake exerts beneficial effects primarily in dysregulated, rather than normal, metabolic states.

This mode of action contrasts with that of conventional pharmaceuticals, which generally consist of single, pure chemical compounds that act through defined ligand-receptor interactions [44]. Similarly, functional foods and nutraceuticals are usually understood in terms of specific bioactive components (food factors) that act on defined molecular targets. For example, 1-deoxynojirimycin, an ingredient of Morus alba, a well-known natural resource for treating diabetes, inhibits intestinal α-glucosidase to suppress postprandial glucose spikes [45, 46], and isoliquiritigenin from licorice, which inhibits matrix metalloproteinases via the JNK and p38 MAPK pathways [47]. In contrast, our findings indicate that the mode of action of T. magnatum mycelium extract differs from these, and is more likely to act indirectly. Our preliminary unpublished data and a recent metaborome study reported elsewhere [48] of Truffle magnatium extract indicated that the major ingredients are fatty acid analogs such as CLA, and steroids like ergosterol, and failed to identify specific secondary metabolites as candidate active principles. Nevertheless, the direct effect on conventional markers of metabolic syndrome was modest; plasma levels of endocrine and immune regulators—including DHEA, vitamin D3, adiponectin, and NK activity—were significantly increased (Table 1). These components are not intrinsic to truffle mycelium but are well-known to influence glucose homeostasis and systemic metabolic balance [49-53]. Moreover, the effect was most pronounced in individuals with higher HbA1c levels, suggesting that truffle mycelium functions by modulating endocrine pathways under conditions of metabolic dyshomeostasis.

Such an indirect and integrative mechanism may offer a novel strategy for managing metabolic syndrome and type 2 diabetes. While pharmacological agents and functional foods with defined single components play important roles in prevention and treatment [8, 9, 11, 12, 23-25], complementary approaches using foods or nutraceuticals with integrated nutritional and pharmacological functions may be particularly effective in preventive medicine. This is especially relevant at the early, asymptomatic stage known as Mibyou, including prediabetes [17-19, 21]. In contrast, single-target pharmacological compounds may disrupt metabolic networks under otherwise normal physiological conditions, leading to adverse effects [54]. For example, thiazide diuretics prescribed for hypertension can exacerbate metabolic disorders [55], and excessive caffeine intake may negate their beneficial effects [56].

Although the precise mechanisms by which truffle mycelium extract stimulates endocrine and immune components remain unclear, parallels may be drawn with the biguanide drug metformin. Metformin acts through AMP-activated protein kinase (AMPK), a master regulator of energy metabolism that modulates glucose uptake, hepatic gluconeogenesis, inflammation, and insulin sensitivity [57, 58]. Both DHEA [59, 60] and vitamin D [61] are reported to activate AMPK, suggesting that AMPK-mediated regulation may also underlie the effects of truffle mycelium. Indeed, we have observed that truffle mycelium extract improves insulin sensitivity in a manner similar to metformin in a STZ-induced diabetes model in rats [62].

Altered plasma mineral balance is another factor in type 2 diabetes, with metformin reported to reduce Cu and Fe while increasing Zn [63]. In this context, the observed decreases in Fe and ferritin after truffle intake, although not statistically significant, may also be relevant (Supplementary Table 1 and Table 2).

Further studies are needed to elucidate the molecular mechanisms by which truffle mycelium extract induces endocrine and immune factors and to clarify its role in restoring metabolic homeostasis. The contribution of the intestinal microbiota should also be considered, as dysbiosis is strongly associated with obesity and metabolic disorders [64]. Although dietary fibers have not yet been characterized in the present truffle mycelium, mushrooms are a rich source of dietary fibers with prebiotic activity [29]. Therefore, modulation of the gut microbiota represents a plausible additional mechanism of action. Future clinical studies are warranted to confirm the ameliorative potential of truffle mycelium in individuals with elevated HbA1c or type 2 diabetes.

5. Conclusion

The present study demonstrated the homeostatic regulatory function of an aqueous ethanol extract from artificially cultured T. magnatum mycelium. After 12 weeks of extract intake in 20 volunteers, plasma levels of DHEA, 1, 25-dihydroxy vitamin D3, adiponectin, and insulin were significantly elevated, as was NK cell activity. The extract also exhibited protective effects on the liver and kidney. Although the group difference did not reach statistical significance, markers related to metabolic disorder showed a trend toward decreased levels in the higher HbA1c (≥5.9%) group, but not in the lower HbA1c (<5.8%) group. This indicates that the truffle mycelium extract modulates dysregulated metabolic conditions by functioning as a homeostatic modulator.

Further studies are needed to confirm the anti-metabolic disorder effects in individuals with higher HbA1c levels who have been diagnosed with pre-diabetes or type 2 diabetes. Studies are also needed to identify the active component(s) of truffle mycelium and elucidate the mechanisms by which truffle functions as a metabolic regulator.

Nevertheless, this study suggests a novel strategy for developing dietary interventions and functional foods to support the management of Mibyou, including metabolic disorders and type 2 diabetes.

Abbreviations

DHEA	Dehydroepiandrosterone
NK	Natural Killer (cell/activity)
HbA1c	Hemoglobin A1c (glycated Hemoglobin)
BMI	Body Mass Index
OGTT	Oral Glucose Tolerance Test
AUC	Area Under the Curve
MCV	Mean Corpuscular Volume
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
AST	Aspartate Aminotransferase
ALT	Alanine Aminotransferase
LDH	Lactate Dehydrogenase
γGT / γ-GT	Gamma-Glutamyl Transpeptidase (also Written as GGT: Gamma-Glutamyl Transferase)
CPK	Creatine Phosphokinase (older Term)
CK	Creatine Kinase (modern Equivalent; Same Enzyme as CPK)
LDL	Low-Density Lipoprotein (cholesterol)
HDL	High-Density Lipoprotein (cholesterol)
ALP	Alkaline Phosphatase
LD	Lactate Dehydrogenase
A/G	Albumin/Globulin Ratio
STZ	Streptozocin

Supplementary Material

The supplementary material can be accessed at https://doi.org/10.11648/j.jfns.20261404.14

Author Contributions

Tetsuya Konishi: Conceptualization, Formal Analysis, Writing – original draft

Rakan Matsui: Conceptualization, Data curation, Validation

Kennichi Watanabe: Methodology, Validation, Writing – review & editing

Ken Usami: Resources, Validation

Akinori Iguchi: Validation, Writing – review editing

Saori Nakagawa: Validation, Writing – review & editing

Conflicts of Interest

The authors declare no conflict of interest.

References

[1] Magliano DJ, Boyko EJ, IDF Diabetes Atlas 10th edition scientific committee. Brussels: International Diabetes Federation; 2021.

[2] Siam NH, Snigdha N, Tabasumma N, Parvin I, Diabetes Mellitus and Cardiovascular Disease: Exploring Epidemiology, Pathophysiology, and Treatment Strategies. *Rev Cardiovasc Med*. 2024, 25(12): 436. https://doi.org/10.31083/j.rcm2512436

[3] Chen R, Ovbiagele B, Feng W, Diabetes and Stroke: Epidemiology, Pathophysiology, Pharmaceuticals and Outcomes *Am J Med Sci*. 2016, 351(4): 380-386. https://doi.org/10.1016/j.amjms.2016.01.011

[4] Giovannucci E, Harlan DM, Archer MC, et al, Diabetes and Cancer A consensus report *Diabetes Care*. 2010, 33(7): 1674-1685. https://doi.org/10.2337/dc10-0666

[5] Anstey KJ, Ee N, Eramudugolla R, Jagger C, Peters R. A Systematic review of meta-analyses that evaluate risk factors for dementia to evaluate the quantity, quality, and global representativeness of evidence. *J Alzheimers Dis*. 2019, 70(s1): S165-S186. https://doi.org/10.3233/JAD-190181

[6] Banday MZ, Sameer AS, Nissar S, Pathophysiology of diabetes: An overview. *Avicenna J Med.* 2020, 10(4): 174-188. https://doi.org/10.4103/ajm.ajm_53_20

[7] Deng Y, Yang Q, Hao C, et al. Combined lifestyle factors and metabolic syndrome risk: a systematic review and meta-analysis. International Journal of Obesity 2025, 49, 226-236.

[8] Campbell RK, White JR, Saulie BA, Metformin: a new oral biguanide. Clin Ther 1996, 18(3) 360-371.

[9] LaMoia TE, Shulman GI, Cellular and molecular mechanisms of metformin action. *Endocr. Rev*. 2021, 42 (1), 77-96. https://doi.org/10.1210/endrev/bnaa023

[10] Hinnen D, Glucagon-Like Peptide 1 Receptor Agonists for Type 2 Diabetes *Diabetes Spectr*. 2017 30(3): 202-210. https://doi.org/10.2337/ds16-0026

[11] National Kidney Foundation News & Story FDA Approves Ozempic for Type 2 Diabetes and Chronic Kidney Disease February 20, 2025. https://www.kidney.org/news-stories/fda-approves-ozempic-type-2-diabetes-and-chronic-kidney-disease

[12] Monami M, Marchionni N, Mannucci E, Glucagon-like peptide-1 receptor agonists in type 2 diabetes: a meta-analysis of randomized clinical trials. *Eur J Endocrinol*. 2009, 160(6): 909-17.

[13] Valabhji J, Kar P, Rise in type 2 diabetes shows that prevention is more important than ever. *BMJ* 2023, 381. https://doi.org/10.1136/bmj.p910 (Published 25 April 2023).

[14] Ke SX, The principles of health, illness, and treatment - The key concepts from The Yellow Emperor's Classic of Internal Medicine. *J Ayurv Integr Med* 2023, 14: 100-637.

[15] Lee JC, Kim SH, Lee Y, The concept of Mibyeong (sub-health) in Korea: A Delphi study. *Eur J Integr Med* 2013, 5: 514-518.

[16] Fukuo Y, Destructive creation in the Reiwa Era Utilization of the concept of Modern Mibyou as Presymptomatic Medicine. J Int Soc Inf Sci 2010, 38: 15.

[17] Konishi T, Mibyou Care is a Key for Healthy Life Elongation: The Role of Mibyou-Care Functional Foods. In Complementary Therapies; Bernardo-Filho, M., Ed. 2021, IntechOpen: London, UK.

[18] Konishi T, Mibyou-care Functional Food: Integrated Role and Use of Functional Foods in Mibyou-care. Global J Nutr Food Sci 2024, 4(5). https://doi.org/10.33552/GJNFS.2024.04.000596

[19] Pitsavos C, Panagiotakos D, Weinem M, Stefanadis C, Diet, Exercise and the Metabolic Syndrome. *Rev Diabet Stud.* 2006, 3(3): 118-126. https://doi.org/10.1900/RDS.2006.3.118

[20] Driessche JJvd, Plat J, Mensink RP, Effects of superfoods on risk factors of metabolic syndrome: a systematic review of human intervention trials. Food Funct., 2018, 9, 1944-1966.

[21] Hoyas I, Leon-Sanz M, Nutritional Challenges in Metabolic Syndrome. *J Clin Med*. 2019, 8(9): 1301. https://doi.org/10.3390/jcm8091301

[22] Jennings A, Thompson AS, Tressera-Rimbau A, Flavonoid-Rich Foods, Dementia Risk, and Interactions With Genetic Risk, Hypertension, and Depression. *JAMA Netw Open* Published Online: September 18, 2024, 7;(9): e2434136. https://doi.org/10.1001/jamanetworkopen.2024.34136

[23] Derosa G, D'Angelo A, Angelini F, et al, Nutraceuticals and Supplements in Management of Prediabetes and Diabetes. *Nutrients* 2025, *17*(1), 14. https://doi.org/10.3390/nu17010014

[24] Derosa G, CLimas CP, Macas PC, Estrella A, Maffioli P, Dietary and nutraceutical approach to type 2 diabetes. *Arch Med Sci* 2014, 10, 2: 336-344. https://doi.org/10.5114/aoms.2014.42587

[25] Davì G, Santilli F, Patrono C, Nutraceuticals in Diabetes and Metabolic Syndrome. *Cardiovascular Therapeutics* 2010, 28, 185-254.

[26] Rodrigues EL, Marcelino G, Silva GT, et al, Nutraceutical and Medicinal Potential of the Morus Species in Metabolic Dysfunctions *Int. J. Mol. Sci* 2019, 20, 301. https://doi.org/10.3390/ijms20020301

[27] Abdulghani MF, Al-Fayyadh S, Natural products for managing metabolic syndrome: a scoping review *Front Pharmacol* 2024, 15: 1366946. https://doi.org/10.3389/fphar.2024.1366946

[28] Gupta G, Rustagi S, Exploring the Potential of Nutraceutical Foods Prepared from Rice Bran Oil, Flaxseed, and Barley Combination through Extrusion Technology: An Updated Review. *Natural Resources for Human Health* 2025, 5, 484-498. https://doi.org/10.53365/nrfhh/204287

[29] Chugh RM, Mittal P, Tanu NMP, Tanima A, et al, Bhattacharya, Hitesh Chopra, Simona Cavalu, Rupesh K. Gautam, Fungal Mushrooms: A Natural Compound With Therapeutic Applications. Front. Pharmacol 2022, Vol 13 – 2022. https://doi.org/10.3389/fphar.2022.925387

[30] Matsugo S, Toshio Sakamoto T, Wakame K, et al, Mushrooms as a Resource for Mibyou-Care Functional Food; The Role of Basidiomycetes-X (Shirayukidake) and Its Major Components. *Nutraceuticals* 2022, *2*(3), 132-149. https://doi.org/10.3390/nutraceuticals2030010

[31] Luo J, Ganesan K, Xu B, Unlocking the Power: New Insights into the Anti-Aging Properties of Mushrooms *J Fungi* (Basel). 2024, 10(3): 215. https://doi.org/10.3390/jof10030215

[32] Bhambri A, Srivastava M, Vivek G Mahale Mahale VG, et al, Mushrooms as Potential Sources of Active Metabolites and Medicines. *Front Microbiol* 2022, 13: 837266. https://doi.org/10.3389/fmicb.2022.837266

[33] Valverde ME, Hernández-Pérez T, Paredes-López O, Edible Mushrooms: Improving Human Health and Promoting Quality Life. *Int J Microbiol* Vol 2015, Article ID 376387, 14 pages. http://dx.doi.org/10.1155/2015/376387

[34] Allen K, Bennett JW, Tour of Truffles: Aromas, Aphrodisiacs, Adaptogens, and More. *Mycobiology* 2021, 49(3): 201-212. https://doi.org/10.1080/12298093.2021.1936766

[35] Dahham SS, Al-Rawi SS, Ibrahim AH, et al, Antioxidant, anticancer, apoptosis properties and chemical composition of black truffle *Terfezia claveryi* Saudi Journal of Biological Sciences 2018, 25, 1524-1534.

[36] Wu Z, Jayachandran M, Cheang WS, Xu B, Black Truffle Extract Exerts Antidiabetic Effects through Inhibition of Inflammation and Lipid Metabolism Regulation. *Oxid Med Cell Longev* 2022, 2022: 6099872. https://doi.org/10.1155/2022/6099872

[37] Zhang T, Jayachandran M, Ganesan K, Xu B, The Black Truffle, Tuber melanosporum (Ascomycetes), Ameliorates Hyperglycemia and Regulates Insulin Signaling Pathway in STZ-Induced Diabetic Rats. *Int J Med Mushrooms* 2020, 22(11): 1057-1066. https://doi.org/10.1615/IntJMedMushrooms.2020036355

[38] Nakajima K, Nakagawa S and Konishi T, Manipulation of Plasma Dehydroepiandrosterone (DHEA) by Truffle and the Cultured Mycelium: BRM-like Function of Truffles. *Austin Food Sci* 2019, 4(1): 1032.

[39] Karbowska J, Kochan Z, Effects of DHEA on metabolic and endocrine functions of adipose tissue. *Horm Mol Biol Clin Investig* 2013, 14(2): 65-74. https://doi.org/10.1515/hmbci-2013-0009

[40] McNelis JC, Manolopoulos KN, Gathercole LL, et al, Dehydroepiandrosterone exerts antiglucocorticoid action on human preadipocyte proliferation, differentiation, and glucose uptake. Am J Physiol Endocrinol Metab. 2013, 305(9): E1134-E1144. https://doi.org/10.1152/ajpendo.00314.2012

[41] Rasmuson S, Näsman B, Olsson T, Increased serum levels of dehydroepiandrosterone (DHEA) and interleukin-6 (IL-6) in women with mild to moderate Alzheimer's disease. International Psychogeriatrics 2011, 23(9), 1386-1392.

[42] Guo F, Moellering DR, Garvey WT, Use of HbA1c for Diagnoses of Diabetes and Prediabetes: Comparison with Diagnoses Based on Fasting and 2-Hr Glucose Values and Effects of Gender, Race, and Age. Metab Syndr Relat Disord 2014, 12(5): 258-268. https://doi.org/10.1089/met.2013.0128

[43] Heianza Y, Hara S, Arase Y, et al, HbA1c 5.7-6.4% and impaired fasting plasma glucose for diagnosis of prediabetes and risk of progression to diabetes in Japan (TOPICS 3): a longitudinal cohort study. *Lancet* 2011, 378: 147-55 Published Online June 25, 2011. https://doi.org/10.1016/S0140-6736(11)60472-8

[44] Zheng S, Zou M, Yingfeng Shao Y, et al, Two-dimensional measurements of receptor-ligand interactions. *Front. Mol. Biosci*., 2023, 10 – 2023. https://doi.org/10.3389/fmolb.2023.1154074

[45] Yoshikuni Y, α-Glucosidase Inhibitor, 1-Deoxynojirimycin and its N-Substituted Derivatives as Anti-Diabetic Agents or Anti-Human Immunodeficiency Virus Agents. *TIGG* 1991, 3(11) 184-192.

[46] Nakamura M, Nakamura S, Oku T, Suppressive response of confections containing the extractive from leaves of *Morus Alba* on postprandial blood glucose and insulin in healthy human subjects. Nutrition & Metabolism 2009, 6: 29. https://doi.org/10.1186/1743-7075-6-29

[47] Kang SW, Choi JS, Choi YJ, et al, Licorice isoliquiritigenin dampens angiogenic activity via inhibition of MAPK-responsive signaling pathways leading to induction of matrix metalloproteinases. *J Nutr Biochem* 2010, 21, 55-65.

[48] Angeloni S, Morconi R, Pitti D, et al, Italian White Truffle (Tuber magnatum Pico): Discovery of new molecules through untargeted UHPLC-QTOF-MS analysis. Food chem. 2025, 477, 143562. https://doi.org/10.1016/j.foodchem.2025.143562

[49] Yanase T, Muta K, Nawata H, DHEA: Effects on oxidative and glycative stress and glucose metabolism. Glycative Stress Research 2020, 7, 42-49. https://doi.org/10.24659/gsr.7.1_42

[50] Yaribeygi H, Maleki M, Sathyapalan T, et al, The molecular mechanisms by which vitamin D improve glucose homeostasis: A mechanistic review. Life Sciences 2020, 244, 117305. https://doi.org/10.1016/j.lfs.2020.117305

[51] Farahmand MA, Daneshzad E, Teresa T. Fung Fung TT, et al, What is the impact of vitamin D supplementation on glycemic control in people with type-2 diabetes: a systematic review and meta-analysis of randomized controlled trails. BMC Endocrine Disorders 2023, 23, Article number: 15. https://doi.org/10.1186/s12902-022-01209-x

[52] Tao C, Sifuentes A, Holland WL, et al, Regulation of glucose and lipid homeostasis by adiponectin: effects on hepatocytes, pancreatic β cells and adipocytes. Best Pract Res Clin Endocrinol Metab. 2014, 28(1): 43-58. https://doi.org/10.1016/j.beem.2013.11.003

[53] Pidugu VK, Kostic TS, Andric SA, et al, Systemic regulation of organ homeostasis and implications of hormones and immunity, Volume II. *Front. Endocrinol* 2023, 26; 14 – 2023. https://doi.org/10.3389/fendo.2023.1235274

[54] Zhang KK, Chen LJ, Li JH, et al, Methamphetamine Disturbs Gut Homeostasis and Reshapes Serum Metabolome, Inducing Neurotoxicity and Abnormal Behaviors in Mice. *Front Microbiol* 2022, 13: 755189. https://doi.org/10.3389/fmicb.2022.755189

[55] Reungjui S, Roncal CA, Mu Wei, et al, Thiazide diuretics exacerbate fructose-induced metabolic syndrome. J Am Soc Nephrol 2007, 18(10): 2724-31. https://doi.org/10.1681/ASN.2007040416

[56] Reddy VS, Shiva S, Manikantan S, Ramakrishna S, Pharmacology of caffeine and its effects on the human body. Eur J Med Chem Rep 2024, 10, 100138. https://doi.org/10.1016/j.ejmcr.2024.100138

[57] Zhou G, Myers R, Y Li Li Y, et al, Role of AMP-activated protein kinase in mechanism of metformin action. J Clin Invest 2001, 108(8): 1167-74. https://doi.org/10.1172/JCI13505

[58] Li Z, Liu L, Yang Y, et al, Metformin ameliorates senescence of adipose-derived mesenchymal stem cells and attenuates osteoarthritis progression via the AMPK-dependent autophagy pathway. Oxid. Med. Cell Longev. 2022, 4620254. https://doi.org/10.1155/2022/4620254

[59] Yokokawa T, Sato K, Nobumasa Iwanaka Iwanaka N, et al, Dehydroepiandrosterone activates AMP kinase and regulates GLUT4 and PGC-1α expression in C2C12 myotubes Biochem Biophys Res Commun 2015, 463(1-2): 42-7. https://doi.org/10.1016/j.bbrc.2015.05.013

[60] Yamashita R, Saito T, Satho S, et al, Effects of Dehydroepiandrosterone on Gluconeogenic Enzymes and Glucose Uptake in Human Hepatoma Cell Line, HepG2. Endocrine Journal 2005, 52(6) 727-733. https://doi.org/10.1507/endocrj.52.727

[61] Chang E, Vitamin D Mitigates Hepatic Fat Accumulation and Inflammation and Increases SIRT1/AMPK Expression in AML-12 Hepatocytes Molecules 2024, 29(6), 1401; https://doi.org/10.3390/molecules29061401

[62] Iwasa K, Suzuki H, Ishiguro T, et al, Anti-diabetes function of truffle mycelium extract studied in STZ-diabetes rat model. 22th Japan Medical Functional Food Society Annual Meeting, O-36, 2025.

[63] Otowa-Suematsu N, Sakaguchi K, Yamada T, et al, Association of metformin treatment with changes in metal dynamics in individuals with type 2 diabetes. BMJ Open Diabetes Res Care 2025 13: e005255. https://doi.org/10.1136/bmjdrc-2025-005255

[64] Amabebe E, Robert FO, Agbalalah T, Orubu ESF, Microbial dysbiosis-induced obesity: role of gut microbiota in homeostasis of energy metabolism. Brit J Nutrit 2020, 123(10); 1127-1137. https://doi.org/10.1017/S0007114520000380