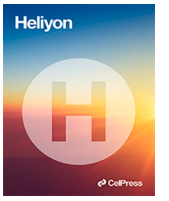
Heliyon 9 (2023) e13217

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

5-Hydroxymethylfurfural induces mice frailty through cell senescence-associated sarcopenia caused by chronic inflammation

Ting Xu [a], Rong Xia [b,c], Fan He [a], En-Hui Dong [a], Jie-Miao Shen [a], Chang-Chang Xu [a], Ming-Hui Ji [a,**], Qin Xu [a,*]

[a] School of Nursing, Nanjing Medical University, 101 Longmian Avenue, Nanjing, 211166, PR China
[b] Key Lab of Modern Toxicology of Ministry of Education, Center for Global Health, School of Public Health, Nanjing Medical University, 101 Longmian Avenue, Nanjing, 211166, PR China
[c] Department of Respiratory and Critical Care Medicine, Jiangsu Province Hospital, Nanjing, 210029, PR China

ARTICLE INFO

Keywords:
5-Hydroxymethylfurfural
Cell senescence
Frailty
Inflammation

ABSTRACT

Objective: 5-Hydroxymethylfurfural (5-HMF) is an important component of air pollution, confirmed to be a risk factor for pulmonary inflammation. However, its association with general health is unknown. This article aimed to clarify the effect and mechanism of 5-HMF in the occurrence and aggravation of frailty in mice by investigating whether exposure to 5-HMF was linked to the occurrence and aggravation of mice frailty.

Methods: Twelve male C57BL/6 mice (12-month-old, 38 ± 1 g) were randomly divided into the control group and the 5-HMF group. The 5-HMF group was treated with 5-HMF (1 mg/kg/day, respiratory exposure) for 12 months, whereas the control group was treated with equal amounts of sterile water. After the intervention, the ELISA method was used to detect the serum inflammation level of the mice, and the physical performance and frail status were evaluated using a Fried physical phenotype-based assessment tool. The differences in the body compositions were calculated from their MRI images, and the pathological changes in their gastrocnemius muscle were revealed using the H&E staining. Furthermore, the senescence of skeletal muscle cells was evaluated by measuring the expression levels of senescence-related proteins by the western blotting.

Results: In the 5-HMF group, serum inflammatory factors IL-6, TNF-α, and CRP levels were significantly raised ($p < 0.01$). Mice in this group had higher frailty scores and significantly reduced grip strength ($p < 0.001$), slower weight gains, less WVgastrocnemius muscle masses, and lower sarcopenia indices (SI). In addition, the cross-sectional areas of their skeletal muscles were reduced, and the levels of their cell senescence-related proteins (p53, p21, p16, SOD1, SOD2, SIRT1, SIRT3) were considerably altered ($p < 0.01$).

Conclusion: 5-HMF may induce chronic and systemic inflammation, which in turn accelerates the progression of the frailty of mice through cell senescence.

* Corresponding author.
** Corresponding author..
E-mail addresses: tingxu1229@stu.njmu.edu.cn (T. Xu), XRong1008@163.com (R. Xia), fanhe@stu.njmu.edu.cn (F. He), dongenhui@stu.njmu.edu.cn (E.-H. Dong), jiemiao_shen@163.com (J.-M. Shen), xcc0815@stu.njmu.edu.cn (C.-C. Xu), jiminghui77@sina.com (M.-H. Ji), qinxu@njmu.edu.cn (Q. Xu).

https://doi.org/10.1016/j.heliyon.2023.e13217
Received 20 October 2022; Received in revised form 11 January 2023; Accepted 20 January 2023
Available online 22 January 2023

1. Introduction

According to the World Health Organization, the global population of older adults reached 1 billion in 2019 and is expected to double to 2.1 billion in the coming three decades by 2050 [1]. The 'grim' global aging situation has become a more severe problem accompanied by an increase in elderly adults with frailty [2]. Referring to unhealthy accelerated aging and increased vulnerability due to the cumulative damage of multiple systems [3], frailty has drawn great attention because it results in rising risk of adverse health events, such as falls, delirium, disability, hospitalization, and early mortality in the elderly [4]. The ratios of frailty and pre-frailty among the elderly population today have reached 4.9–27.3% and 34.6–50.9%, respectively. Despite the fact that frailty has been a common issue, the causes of frailty remain unclear, which hinders the development of detecting and preventing frailty-related healthcare issues among the elderly. Therefore, exploration of the causes of frailty is of great significance in promoting healthy aging [2,5].

Studies have shown that air pollution is an important and reversible factor [6] that is closely associated with the risk of frailty [7,8] and sarcopenia, while the exact component and mechanisms have not been described. 5-Hydroxymethylfurfural (5-HMF) is a crucial component of air pollution [9,10], a heterocyclic compound formed during heating carbohydrates through the Maillard reaction [11–13], commonly found in the production of processed foods or combustion of chemical products that contain sugar. Previous studies pointed out that pro-inflammatory effects, such as elevated interleukin-6 levels, may be associated with frailty. At the same time, 5-HMF has an inflammation-induction effect [9], which is known to be the core pathological basis of frailty by damaging the abilities of physical activities, and altering the muscle weight and strength [10]. Studies on 5-HMF are intriguing and need to be explored when accounting for air pollution-related frailty and other health deficiencies.

It is reported that inflammation could result in cellular senescence, a permanent state of cell growth stagnation, and cell cycle disorder [14]. Meanwhile, strong evidence demonstrates that cell senescence is the promising mechanism of age-related frailty and other diseases [15–17] and is proposed to be a plausible link between inflammation [18]and sarcopenia [19,20] tissue degeneration [14], anabolic muscle resistance [21] under the control of senescence-related proteins, among which, p53 protein plays an essential role in the regulation of the innate immune system and cell response in aging and frailty [22]. It has been confirmed that 5-HMF could trigger cell damage by activating the death receptor and mitochondrial pathways [23], while whether 5-HMF could affect cell senescence remains unclear. Consequently, we assumed that chronic inflammation caused skeletal muscle cell senescence, aggravating the inflammation and dysfunction of muscle, thus leading to some frailty characteristics. To confirm our hypothesis, we also detected the p53 protein and some other proteins related to cellular senescence. In summary, we proposed that 5-HMF could lead to chronic and system inflammation, consequently playing an essential role in frailty.

This study aimed to elucidate the effects of 5-HMF on the onset and exacerbation of frailty in mice and to determine its mechanism of action, which will help provide new theoretical support for the prevention and treatment of frailty. An animal model of long-term respiratory exposure to 5-HMF was established to study the effects of 5-HMF on the mice. This study was designed to provide novel insights into the relationship between 5-HMF and frailty and provide new theoretical support for the prevention and treatment of frailty.

2. Materials and methods

2.1. Animal treatment

Twelve male C57BL/6 mice were acquired from Shanghai SLAC Laboratory Animal Co., Ltd. (Shanghai, China). The mice were housed in standard cages in a pathogen-free animal room at a temperature of 22 ± 2 °C and humidity of 55 ± 5% in the animal core facility of Nanjing Medical University. The mice were fed a regular diet for 12 months before the experiment. Twelve mice with the same body weight (38 ± 1 g) were selected and randomly divided into two groups for the further experiment: the control group (n = 6) and the intervention group (n = 6). The intervention group was given 5-HMF solution atomization inhalation (Sigma-Aldrich, St. Louis, MO, USA) 1mg/k/day for one year of chronic inhalation exposure. The dose was administered as described in our previous study [9]. The control mice were given an inhalation of distilled water, and a regular diet (food and drinking water) was given to both groups.

The present study was approved by the Ethical Committee of Nanjing Medical University (approval No. IACUC-2109037). All procedures were conducted under the national standard of Laboratory animal -Guideline for ethical review of animal welfare (GB/T 35892–2018) and Guide for the Care and Use of Laboratory Animals: Eighth Edition. All attempts were made to minimize animal suffering.

2.2. Frailty criteria measurement

The frailty assessment of mice consists of four functional tests, including grip strength, walking speed, endurance, and physical activity ability, following Liu et al. [24]. A mouse was assigned a positive frailty marker for each functional test if its score was one standard deviation below the average [25]. A mouse was identified as frail if having three or more markers and was identified as pre-frail if having two.

2.2.1. Criterion 1: grip strength

Grip strength was evaluated using a grip meter (P/N760483, Whitehall PA, Colombia). The mouse for evaluation was gently placed on the grip board with its front and hind paws gripped the grid. After gripping, the mouse would have its tail pulled back gradually and

steadily, keeping its torso in a horizontal position. Once either of the mouse's paws was released, the software generated a process of unloading because of the contracting of paws, and the grip strength was recorded in Newton(N). Each mouse performed five trials with a 10-min rest period between every two consecutive trials. The average grip strength was calculated after removing the highest and lowest score and was recorded as the final score.

2.2.2. Criterion 2: walking speed

Walking speed was assessed using a rotarod (Model: 80820F, Lafayette Instruments, Lafayette, IN). Mice were allowed to have warmed-up tests for three days (3 trials per day) before having the real test on the fourth day. During testing, a mouse was placed on the rotarod with the piston rotating at an initial speed of 4 rpm and an acceleration of 7.2 rpm/minutes^2 (accelerated to 40 rpm in 5 min). Rotational speed was recorded when the mice fell. Moreover, three measurements were averaged with 20-min intervals between each measurement. The best scores of these trials were recorded as results.

2.2.3. Criterion 3: endurance

Mice's endurance was evaluated using a motorized treadmill (Exer 3/6 Treadmill; Columbus, OH), as described by Seldeen et al. [26]. Mice were allowed to practice on the equipment for three days (3 trials per day) before the actual test. On the fourth day, a mouse was first placed on the treadmill moving at a speed of 5 m/min for a 5-min warm-up. Afterward, the treadmill's speed increased at an acceleration of 1 m/min^2. The fatigue time was recorded when the mouse was unable to keep up with the treadmill for the third time (e.g., the mice stayed on the back of the treadmill for 3 s without trying to run again was recorded as one failure). Three trials were taken with 20-min intervals in between. The average fatigue time of a mouse was recorded as the final score of its endurance assessment.

2.2.4. Criterion 4: physical activity

Mice's activity was assessed by recording their daily physical activity level using a voluntary running wheel [24] (Model: 80820F, Lafayette Instruments, Lafayette, IN). Each mouse was housed in cages with a running wheel for four days. The distance traveled in revolutions was measured and converted to kilometers. The average distance a mouse traveled per day was used as its physical activity assessment score.

2.3. Body composition analysis

MRI scans (Parallel T2WI scans) were performed using a small animal magnetic resonance apparatus (Bruker BioSpec USR 70/20, Paravision 6.0.1, Germany) in the animal core facility of Nanjing Medical University. 4% isoflurane was used for the first anaesthetization, and 1.5% isoflurane was used for anesthesia maintenance. The same parameters were applied to both groups during scanning in each group. The threshold segmentation method was used to segment and process fat and muscle parts, and the threshold setting range of adipose tissue in different pictures was adjusted according to anatomical knowledge. MATLAB was used to obtain the pixel area of each tissue in the picture and calculate the volume to obtain fat mass according to the finite element method.

2.4. Skeletal muscle processing and hematoxylin-eosin staining

The following procedure was taken to measure the muscle weight. The skin and fascia at the back of each mouse calf were first cut with scissors, exposing the gastrocnemius muscle, which was detached from the mouse's body by cutting from the middle of the achilles tendon. The proximal gastrocnemius muscle attachment was also cut and removed. The wet weight of muscles was measured. The sarcopenia index (SI) was calculated by the ratio of gastrocnemius muscle mass (g) to body mass (g). The gastrocnemius muscle was cut in the midline in the direction of the fiber of the dilutes and fixed in 10% formaldehyde for 48 h. Then, it is dehydrated and immersed in wax for H&E staining to analyze the pathological change of muscle tissues with a thickness of 5 μm. Finally, the cross-sectional muscle area and myofibroblasts' morphological changes were analyzed by digital slides and Image J software.

2.5. Western blot assay

Following weight measurements and H&E staining, western blotting was performed to analyze the expression levels of proteins in muscles. The gastrocnemius muscle obtained previously was rapidly frozen in liquid nitrogen and then cut into pieces. The total protein of mice muscle tissue was extracted by RIPA with a proportion of 1 mg tissue: 200 μl RIPA. Western blot analysis was performed using SIRT1, SIRT3, p53, p21, p16, SOD1, SOD2, and β-actin primary antibody (Abcam, USA). Quantitative analysis was performed using corresponding secondary antibody incubation, chemiluminescence imaging, and Image J analysis.

2.6. Serum inflammatory factors levels measurement

Serum inflammatory level was measured because it is a strongly correlated indicator of frailty. The blood sample was collected from mice under carbon dioxide anesthesia (3000 g, 4 °C, 10 min) for pain alleviation. Next, the serum inflammatory factors IL-6, TNF-α, and CRP were measured using an ELISA kit (cat. No. PI326, Beyotime Biotechnology, Shanghai, China).

2.7. Statistical analysis

Statistical results to be reported were generated from statistical analysis performed using *SPSS version 20.0* (IBM Corp., Armonk, NY, USA). Body weight, gastrocnemius muscle mass, sarcopenia index, and fat content of mice were expressed as the mean ± standard deviation (S.D.) and were compared with Student-Newman-Keuls tests. The frailty scores were compared using the rank sum test, and $p < 0.05$ was considered statistically significant for differences.

3. Results

3.1. 5-HMF causes general chronic inflammation

In this study, we tested serum systemic inflammatory factors IL-6, TNF-α, and CRP using ELISA kits. We found that the serum inflammatory factor levels were significantly increased in the 5-HMF group compared to the control group (Fig. 1A–C). The difference was statistically significant to prove the systemic inflammation induced by lung injury after long-time exposure to 5-HMF ($p < 0.01$).

3.2. 5-HMF aggravates mice's frail tendency by decreasing the grip strength, walking speed, and endurance

Fried frailty phenotype criteria were used to assess the level of mice's frailty (Fig. 2F). In the 5-HMF group, grip strength (control group: 1.85 ± 0.05627 N, 5-HMF group: 1.3 ± 0.07746 N, p = 0.0002), walking speed (maximum rotarod speed) (control group: 32.47 ± 1.654 m/s, 5-HMF group: 28.45 ± 1.202 m/s, p = 0.1186), endurance (total time running) (control group: 838.5 ± 134.6 s, 5-HMF group: 728.5 ± 112.9 s, p = 0.1186) and physical activity (daily distance traveled) (control group: 2.083 ± 0.09482 km/day, 5-HMF group: 1.685 ± 0.1026 km/day, p = 0.1286) were decreased by 13.7%, 4.8%, 7.3%, respectively (Fig. 2A–D). Mice in the 5-HMF group had higher overall frailty scores than mice in the control group (control group: 0, 5- HMF group: 1.333 ± 0.4216, p = 0.0101) (Fig. 2E).

3.3. 5-HMF alters frailty-related body composition and significantly reduces mice gastrocnemius muscle mass

Comparing the body weight and body composition of mice from the two groups, we found the 5-HMF group mice had a lower average body weight (control group: 42.94 ± 0.97 g, 5-HMF group 37.43 ± 0.99 g, $p = 0.0026$) (Fig. 3A), a lower average gastrocnemius muscle mass (control group: 372.6 ± 11.46 mg, 5-HMF group: 268 ± 15.64 mg, $p = 0.0006$) (Fig. 3B), and a lower average sarcopenia index (SI) (control group: 0.8693 ± 0.02897, 5-HMF group: 0.7169 ± 0.03931, $p = 0.0109$) (Fig. 3C) than the control group mice.

Using MRI to analyze the whole-body composition of mice, we found a slight increase in whole-body fat mass of the mice from the 5- HMF group and an increase in body fat percentage (control group: 18.63 ± 0.983; 5-HMF group: 25.65 ± 0.967, $p = 0.0005$) (Fig. 4A–C) compared to those from the control group.

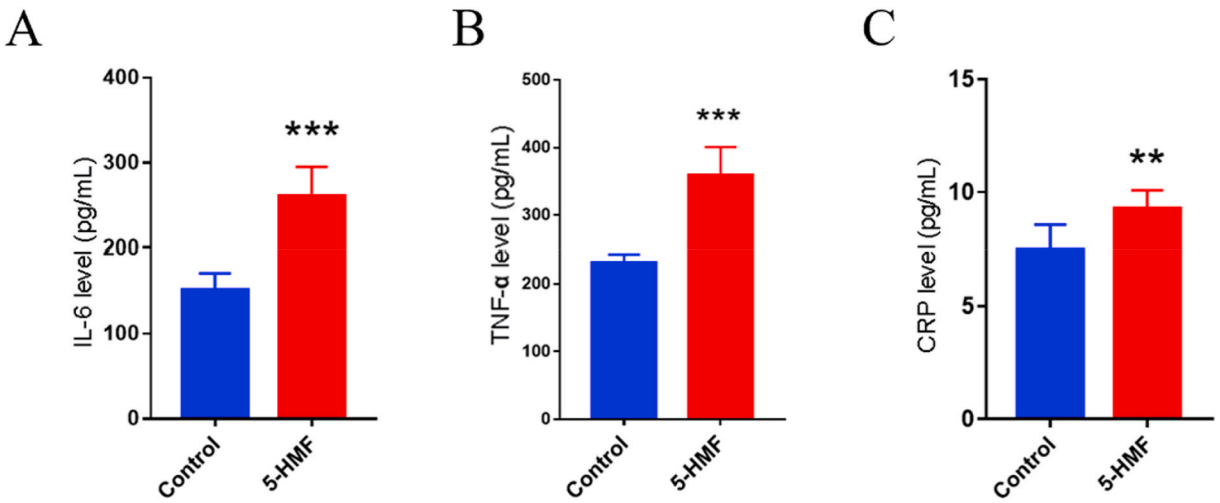


Fig. 1. The effect of 5-HMF on the expression of serum IL-6 (A), TNF-α (B) and CRP (C) after 12-month-5-HMF-exposure. The concentration of IL-6, TNF-α and CRP in the culture medium was analyzed using the respective ELISA kits, respectively. Data were expressed as means ± SDs (n = 6). ***$p < 0.001$.

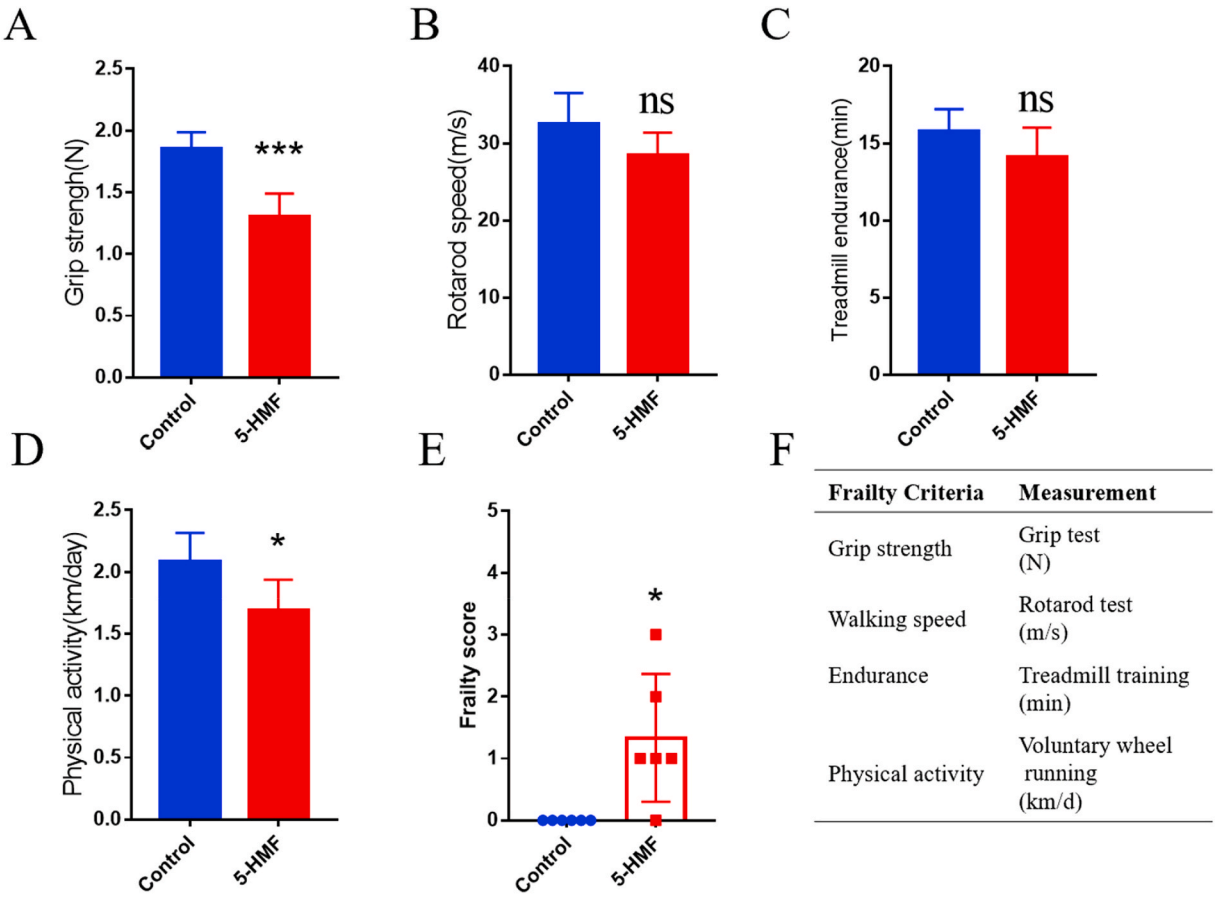


Fig. 2. Changes in frail status accessed by grip strength, endurance, walking speed, and physical activity of mice. (A) Assessment of grip strength of mice whereby mice were pulled away from a grid attached to a force meter and software until a release of paw. (B) Assessment of rotarod speed whereby mice were tested with a rotarod speed increase from 4 to 40 rpm/min over 5 min. (C) Assessment of Endurance by putting mice on treadmill belts with an initial speed of 5 m/min and an acceleration of 1 m/min ^{2}; (D) Assessment of physical activity by using a voluntary running wheel to record the distance. ϵ Changes in frailty scores in mice. Frail status was evaluated by 5 parameters, including unexpected weight loss, grip strength, rotarod speed, endurance, physical activities, mice exhibited three or more assessments below cohort-determined cutoff levels was frail and prefrail if below cutoff in 1 or 2 parameters. (F) Four frailty criteria including grip strength, walking speed, physical activity, and endurance are selected according to Liu [24].*$p < 0.05$, ***$p < 0.001$, ns $p > 0.05$.

3.4. Aerosol inhalation of 5-HMF can change the morphology of mice gastrocnemius muscle cells and reduce the cross-sectional area of fibroblasts

Our experiments showed that 5-HMF significantly reduced mice gastrocnemius muscle mass (control group: 334.1 ± 11.87 mg, 5 -HMF group: 243.6 ± 14.22 mg, $p = 0.0006$). The effect of 5-HMF inhalation on fibroblast morphology (Fig. 5AB) showed that 5-HMF changed the gastrocnemius muscle structure and cell morphology and significantly reduced the cross-sectional area of the gastrocnemius muscle in mice (Fig. 5C) (control group: 883.3 ± 30.09 μm^2, 5-HMF group: 729.2 ± 29.54 μm^2, $p = 0.0009$).

3.5. Respiratory exposure to 5-HMF induces muscle cell senescence and SASP

To determine whether 5-HMF-induced frailty is related to skeletal muscle cell senescence and SASP, we investigated SASP-related parameters in this study. We detected the expression of senescence protein and measured the protein levels of SIRT1, SIRT3, p53, p21, p16, SOD1, and SOD2. Proteins p53, p21, p16, SOD1, and SOD2 were significantly higher when protein SIRT1 and SIRT3 were significantly lower in the 5-HMF group than in the control group (Fig. 6). These results suggest that frailty induced by 5-HMF may be associated with senescence of skeletal muscle cells and increased SASP.

4. Discussion

Air pollution is an essential and reversible factor [6] closely associated with the risk of frailty [8] and sarcopenia. A cross-sectional

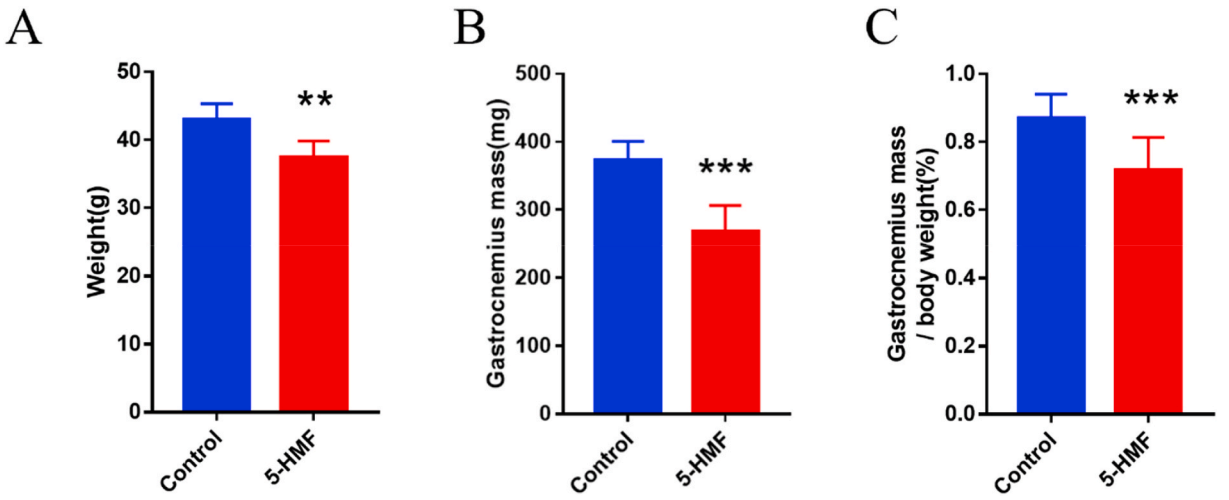


Fig. 3. Changes in body composition of mice were measured after a 12-month-intervention. (A) Body weight measured by an electronic analytical balance, (B) Gastrocnemius muscle were measured after tissue separation, (C) Sarcopenia index was calculated by percentage of gastrocnemius weight in body weight (%). $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, ns $p > 0.05$.

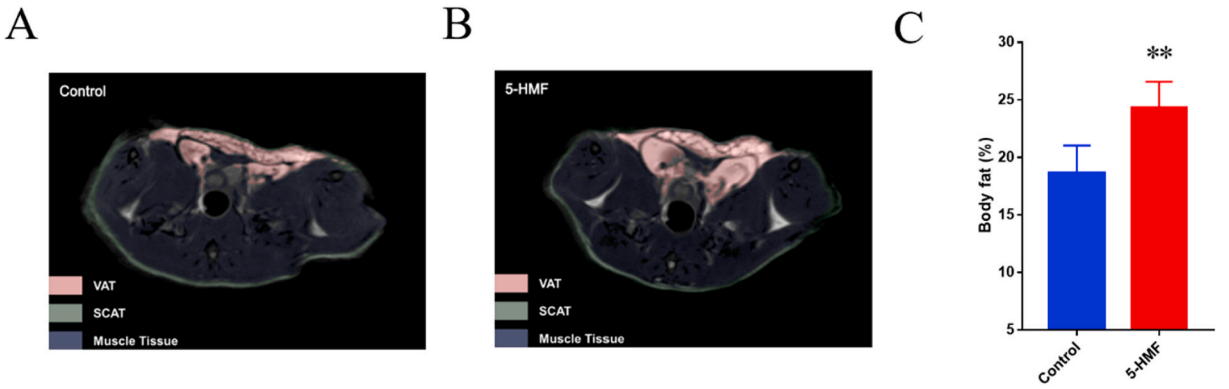


Fig. 4. Extract image fat information MRI-based segmentation in mice treated with 5-HMF. (A) Representative example for axial slice of abdomen segmentation of control (left) mice and 5-HMF intervention mice (right). Delineated segments of visceral adipose tissue (VAT, indicated in red), subcutaneous adipose tissue (SCAT, indicated in green) and muscle tissue (are shown indicated in purple). (B) Fat/body mass ratio calculated by MMRI.$^{*}p < 0.05$. . (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

study of 20,606 older adults by Taiwanese researchers confirmed a significant relationship between air pollution exposure and the prevalence of frailty [27]. Studies demonstrated that acting as the main air pollution components, cigarette smoke, wood, and some other solid fuel combustion products [28] were highly associated with the development and deterioration of frailty by doubling the risk of frailty [8]. 5-HMF is an organic substance that exists in cigarette smoke, food processing, and the combustion of sugar-containing chemical products [15], such as coffee (300–1900 mg/kg) [29], dried fruit (1600–3520 mg/kg) [30], honey (118.47–1139.95 mg/kg) [31], Lactose-free milk (642–2315 μg/kg) [32], cookies (167.4–1100.1 mg/kg) [33], sugar (12.3–23.3 mg/kg), vinegar (316–3250 mg/kg) [34], cigarette smoke (14.1–364.3 μg/puff) [9]. Compared with oral supplementation, respiratory exposure to 5-HMF has been confirmed to have the effect of causing mice chronic inflammatory injury without absorption in the digestive tract and complex metabolic distribution processes [9]. Thus, we hypothesized that the inflammation caused by 5-HMF was one of the significant mechanisms of frailty, which may have beneficial consequences in clarifying and preventing air pollution-related frailty.

Serum IL-6, TNF-α, and CRP [35,36] can lead to unhealthy outcomes such as muscle weakness and decreased activity [10]. Physiological characteristics of frailty can be explained by increased inflammatory factors [37,38]. In our study, we found chronic exposure to 5-HMF could lead to inflammation, altering the frailty features, such as muscle weakness, fatigue, decreased exercise capacity, decreased physical activity, and involuntary weight loss.

The C57BL/6 mice were used for modeling human frailty-related outcomes, and an evaluation of mice frailty developed by frailty phenotype, which has a five-point scale including grip strength, walking speed, endurance, and physical activity, were assessed in this study according to Liu [24] According to the frailty phenotype, mice that match at least three defined criteria are regarded as frail mice, while pre-frailty mice meet two criteria. Our results showed significant differences in mice grip strength ($p < 0.001$), and further

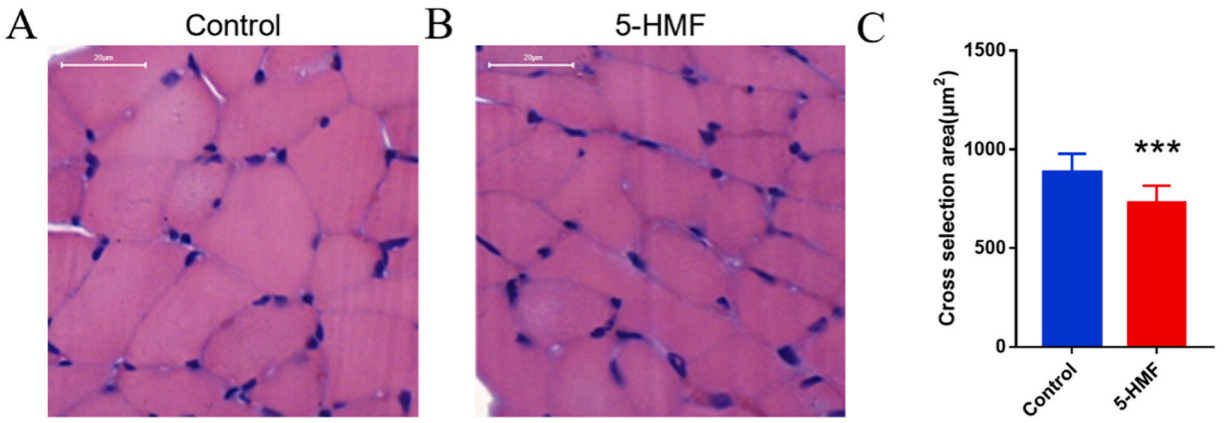


Fig. 5. H&E staining images and cross-sectional area of mice gastrocnemius muscle. The cross-section of myofibroblasts in the gastrocnemius skeletal muscle arranged tightly and regularly in control group, and the nucleus of gastrocnemius muscle fiber cells in the 5- HMF group were loosely arranged, partial cells showed slight hyaline degeneration, and some nuclei showed nuclear inward migration. (A)control group (80 magnification). (B)5-HMF intervention group (80 magnification). (C) changes in the cross-sectional area of the mice gastrocnemius muscle. We There were 6 mice in each group, the right gastrocnemius muscle was used for muscle cross-sectional area analysis. ***$p < 0.001$.

analysis of body composition results showed that 5-HMF significantly reduced mice's body weight ($p = 0.0026$). At the same time, gastrocnemius muscle mass decreased significantly ($p = 0.0006$), which suggested that the effect of 5-HMF on the frailty level of mice was mainly related to the reduction of muscle mass and muscle strength, and further attention needs to be paid to the effect of 5-HMF on body composition, especially on the muscle strength.

Skeletal muscles are critical to controlling movement. Muscle strength and muscle mass partially determine the health status (frailty) and quality of life of the elderly. Progressive decline in muscle mass, strength, and function is characteristic of sarcopenia, a crucial diagnostic condition for frailty and one of the main driving factors. Researchers [39] xenografted senescent cells into skeletal muscles of mice, finding aging muscle cells lead to low muscle fiber cross-sectional area through direct or SASP effect. At the same time, they found a positive correlation and feedback between senescent cell phenotype and sarcopenia cellular markers by measuring the primary aging markers P16 protein and a variety of SASP proteins. In this study, we also found that levels of senescent cell phenotype proteins in mice muscle tissues increased, which may be related to the reduction of fiber cross-sectional areas, and then caused the reduction of muscle strength and muscle mass in the 5-HMF intervention group.

Sarcopenia can lead to a reduction in physical activity and an increase in the risk of obesity, while adipose tissue can enhance systemic and chronic inflammatory responses due to its active endocrine cytokine function. Obesity and sarcopenia are two vehicles for the change in body composition and the loss of physical function [40,41]. Therefore, the relationship between frailty and 'sarcopenic obesity' has also been studied in our research. We used MATLAB to calculate the body composition by obtaining the pixel area of each tissue by MRI and calculating the volume according to the finite element method. MRI is one of the most effective and objective methods for calculating body composition [38]. Our results showed a significant increase in the whole-body fat mass of the mice in the 5-HMF group, especially in the fat/body mass ratio when the body weight had decreased. It is reported that obesity and frailty/-sarcopenia correlate with each other concerning inflammatory pathways. Therefore, these results remind us to explore further the role of inflammatory disorders in obesity and sarcopenia.

As with the majority of studies, there are potential limitations in this study. Firstly, the small sample size is relatively small, and it is necessary to expand the sample size appropriately further to validate the effect of 5-HMF on frailty characteristics and further improve this study's scientific validity. Secondly, we treated mice with only one concentration (1 mg/k/day) of 5-HMF, so we did not obtain the dose-response relationship between 5-HMF and frailty. It is necessary to explore further the exact relationship between the dose of 5-HMF and frailty in future research.

5. Conclusion

In summary, our results revealed that 5- HMF could cause changes in indicators such as body weight, muscle mass, muscle strength, and fat percentage in mice for the potential reason that the increased secretion of inflammatory factors caused by cell senescence-accelerated the catabolism of skeletal muscle, resulting in skeletal muscle atrophy and physical strength. Adverse frailty outcomes such as decreased activity and weight loss confirmed that 5-HMF affected physical activity ability through inflammation, which could be one of the critical mechanisms for air pollution-associated frailty.

Author contribution statement

TingXu: Conceived and designed the experiments, Performed the experiments, Analyzed and interpreted the date, Wrote the paper.
Rong Xia: Analyzed and interpreted the date, Wrote the paper.

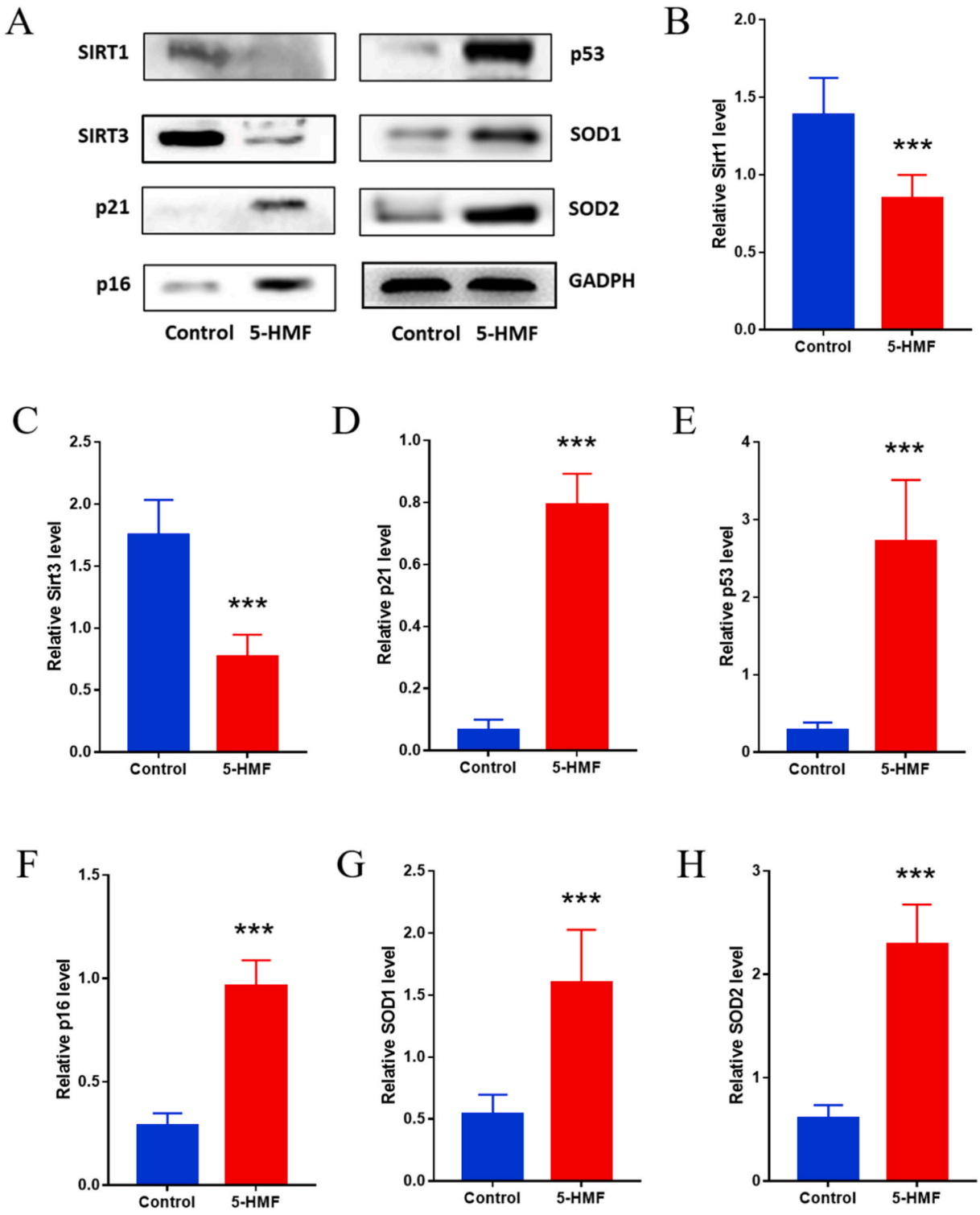


Fig. 6. 5-HMF induces skeletal muscle senescence. Western blotting expression of SIRT1, SIRT3, p21, p16, p53, SOD1 and SOD2 proteins in skeletal muscle tissue. The uncropped images of (A) were referred in Supplemental file. ***$p < 0.001$.

Fan He: Performed the experiments, Analyzed and interpreted the date.
En-Hui Dong; Chang-Chang Xu: Performed the experiments.
Jie-Miao Shen: Analyzed and interpreted the date.

Ming-Hui Ji: Contributed reagents, materials, analysis tools or date; Wrote the paper.
Qin Xu: Contributed reagents, materials, analysis tools or date; Conceived and designed the experiments.

Funding statement

Professor Qin Xu was supported by National Natural Science Foundation of China [No. 82073407], Priority Discipline Development Program of Jiangsu Higher Education Institutions [No. [2018]-No.87], Connotation Construction Project of Nanjing Medical University for Priority Academic of Nursing Science (2022-12).

Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of interest's statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Additional information

No additional information is available for this paper.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.heliyon.2023.e13217.

References

[1] W.H. Organization, ageing-and-health, Available from: https://www.who.int/news-room/fact-sheets/detail/ageing-and-health, 2021.
[2] E. Dent, et al., Management of frailty: opportunities, challenges, and future directions, Lancet 394 (10206) (2019) 1376–1386.
[3] E.O. Hoogendijk, et al., Frailty: implications for clinical practice and public health, Lancet 394 (10206) (2019) 1365–1375.
[4] M. Kameda, et al., Frailty markers comprise blood metabolites involved in antioxidation, cognition, and mobility, Proc. Natl. Acad. Sci. U. S. A. 117 (17) (2020) 9483–9489.
[5] E.H. Gordon, R.E. Hubbard, Differences in frailty in older men and women, Med. J. Aust. 212 (4) (2020) 183–188.
[6] P.J. Landrigan, et al., The Lancet Commission on pollution and health, Lancet 391 (10119) (2018) 462–512.
[7] W.J. Lee, et al., PM(2.5) air pollution contributes to the burden of frailty, Sci. Rep. 10 (1) (2020), 14478.
[8] S. Amiri, S. Behnezhad, Systematic review and meta-analysis of the association between smoking and the incidence of frailty, Neuropsychiatr 33 (4) (2019) 198–206.
[9] M. Ji, et al., Identification of 5-hydroxymethylfurfural in cigarette smoke extract as a new substrate metabolically activated by human cytochrome P450 2A13, Toxicol. Appl. Pharmacol. 359 (2018) 108–117.
[10] X. Zhang, et al., The biology of aging and cancer: frailty, inflammation, and immunity, Cancer J. 23 (4) (2017) 201–205.
[11] Z. Pan, et al., [Research progress of 5-hydroxymethylfurfural, a safety-related substance in traditional Chinese medicine injections], Zhongguo Zhongyao Zazhi 42 (10) (2017) 1842–1846.
[12] J. Granja-Soares, et al., Effect of innovative technology using staves and micro-oxygenation on the odorant and sensory profile of aged wine spirit, Food Chem. 333 (2020), 127450.
[13] V. Moses, et al., Hydroxymethyl furfural (HMF) a high strength cellulose resin for wood composite laminates, Heliyon 8 (12) (2022), e12081.
[14] X. Zheng, et al., Downregulation of HINFP induces senescence-associated secretory phenotype to promote metastasis in a non-cell-autonomous manner in bladder cancer, Oncogene 41 (28) (2022) 3587–3598.
[15] F. Rossiello, et al., Telomere dysfunction in ageing and age-related diseases, Nat. Cell Biol. 24 (2) (2022) 135–147.
[16] J.A. Amorim, et al., Mitochondrial and metabolic dysfunction in ageing and age-related diseases, Nat. Rev. Endocrinol. 18 (4) (2022) 243–258.
[17] N.K. LeBrasseur, T. Tchkonia, J.L. Kirkland, Cellular senescence and the biology of aging, disease, and frailty, Nestle Nutr. Inst. Workshop Ser. 83 (2015) 11–18.
[18] Y. Cai, et al., Elimination of senescent cells by beta-galactosidase-targeted prodrug attenuates inflammation and restores physical function in aged mice, Cell Res. 30 (7) (2020) 574–589.
[19] M. Wan, E.F. Gray-Gaillard, J.H. Elisseeff, Cellular senescence in musculoskeletal homeostasis, diseases, and regeneration, Bone Res. 9 (1) (2021) 41.
[20] P. Sousa-Victor, L. Garcia-Prat, P. Munoz-Canoves, Control of satellite cell function in muscle regeneration and its disruption in ageing, Nat. Rev. Mol. Cell Biol. 23 (3) (2022) 204–226.
[21] C.M. Dungan, et al., Senolytic treatment rescues blunted muscle hypertrophy in old mice, Geroscience 44 (4) (2022) 1925–1940.
[22] A.J. Levine, P53 and the immune response: 40 Years of exploration-a plan for the future, Int. J. Mol. Sci. 21 (2) (2020).
[23] Y. Qiu, et al., 5-Hydroxymethylfurfural exerts negative effects on gastric mucosal epithelial cells by inducing oxidative stress, apoptosis, and tight junction disruption, J. Agric. Food Chem. 70 (12) (2022) 3852–3861.
[24] H. Liu, Clinically relevant frailty index for mice, J. Gerontol. A Biol. Sci. Med. Sci. 69 (12) (2014) 1485–1491.
[25] R.J. Parks, et al., A procedure for creating a frailty index based on deficit accumulation in aging mice, J. Gerontol. A Biol. Sci. Med. Sci. 67 (3) (2012) 217–227.
[26] K.L. Seldeen, et al., Vitamin D insufficiency reduces grip strength, grip endurance and increases frailty in aged C57Bl/6J mice, Nutrients 12 (10) (2020).
[27] W.-J. Lee, et al., PM2.5 air pollution contributes to the burden of frailty, Sci. Rep. 10 (1) (2020), 14478.
[28] L. Cao, et al., Indoor air pollution and frailty: a cross-sectional and follow-up study among older Chinese adults, Environ. Res. 204 (Pt A) (2022), 112006.
[29] S.H. Park, A. Jo, K.G. Lee, Effect of various roasting, extraction and drinking conditions on furan and 5-hydroxymethylfurfural levels in coffee, Food Chem. 358 (2021), 129806.
[30] X. Sun, et al., Content variations in compositions and volatile component in jujube fruits during the blacking process, Food Sci. Nutr. 7 (4) (2019) 1387–1395.

[31] W. Yang, et al., Pathway of 5-hydroxymethyl-2-furaldehyde formation in honey, J. Food Sci. Technol. 56 (5) (2019) 2417–2425.
[32] M. Czerwonka, R. Pietrzak-Sajjad, B. Bobrowska-Korczak, Evaluation of 5-hydroxymethylfurfural content in market milk products, Food Addit. Contam. Part A Chem. Anal. Control Expo Risk Assess 37 (7) (2020) 1135–1144.
[33] B. Svecova, M. Mach, Content of 5-hydroxymethyl-2-furfural in biscuits for kids, Interdiscipl. Toxicol. 10 (2) (2017) 66–69.
[34] P. Liu, et al., Characterization, variables, and antioxidant activity of the maillard reaction in a fructose(-)histidine model system, Molecules 24 (1) (2018).
[35] A.L. Bian, et al., A study on relationship between elderly sarcopenia and inflammatory factors IL-6 and TNF-alpha, Eur. J. Med. Res. 22 (1) (2017) 25.
[36] S. Samaddar, R. Koneri, Polyphenols of marine red macroalga Symphyocladia latiuscula ameliorate diabetic peripheral neuropathy in experimental animals, Heliyon 5 (5) (2019), e01781.
[37] P. Song, J. An, M.H. Zou, Immune clearance of senescent cells to combat ageing and chronic diseases, Cells 9 (3) (2020).
[38] W.M. Thaiss, et al., Noninvasive, longitudinal imaging-based analysis of body adipose tissue and water composition in a melanoma mouse model and in immune checkpoint inhibitor-treated metastatic melanoma patients, Cancer Immunol. Immunother. 70 (5) (2021) 1263–1275.
[39] P.F.L. da Silva, et al., The bystander effect contributes to the accumulation of senescent cells in vivo, Aging Cell 18 (1) (2019), e12848.
[40] A. Kalinkovich, G. Livshits, Sarcopenic obesity or obese sarcopenia: a cross talk between age-associated adipose tissue and skeletal muscle inflammation as a main mechanism of the pathogenesis, Ageing Res. Rev. 35 (2017) 200–221.
[41] G. Livshits, A. Kalinkovich, Inflammaging as a common ground for the development and maintenance of sarcopenia, obesity, cardiomyopathy and dysbiosis, Ageing Res. Rev. 56 (2019), 100980.