



Opinion

Ageing and Obesity Shared Patterns: From Molecular Pathogenesis to Epigenetics

Abdelaziz Ghanemi ^{1,2}, Mayumi Yoshioka ^{1,2} and Jonny St-Amand ^{1,2,*}

- ¹ Functional Genomics Laboratory, Endocrinology and Nephrology Axis, CHU de Québec-Université Laval Research Center, Québec City, QC G1V 4G2, Canada; abdelaziz.ghanemi@crchudequebec.ulaval.ca (A.G.); mayumi.yoshioka@crchudequebec.ulaval.ca (M.Y.)
- ² Department of Molecular Medicine, Faculty of Medicine, Laval University, Québec City, QC G1V 0A6, Canada
- * Correspondence: jonny.st-amand@crchudequebec.ulaval.ca; Tel.: +1-(418)-654-2296

Abstract: In modern societies, ageing and obesity represent medical challenges for healthcare professionals and caregivers. Obesity and ageing share common features including the related cellular and molecular pathways as well as the impacts they have as risk factors for a variety of diseases and health problems. Both of these health problems also share exercise and a healthy lifestyle as the best therapeutic options. Importantly, ageing and obesity also have common epigenetic changes (histone modification, DNA methylation, noncoding RNAs, and chromatin remodeling) that are also impacted by exercise. This suggests that epigenetic pathways are among the mechanisms via which exercise induces its benefits, including ageing and obesity improvements. Exploring these interrelations and based on the fact that both ageing and obesity represent risk factors for each other, would lead to optimizing the available therapeutic approaches towards improved obesity management and healthy ageing.

Keywords: obesity; ageing; epigenetics; pathogenesis; exercise



Citation: Ghanemi, A.; Yoshioka, M.; St-Amand, J. Ageing and Obesity Shared Patterns: From Molecular Pathogenesis to Epigenetics. *Diseases* **2021**, *9*, 87. <https://doi.org/10.3390/diseases9040087>

Academic Editor: Mark Brown

Received: 29 October 2021
Accepted: 28 November 2021
Published: 29 November 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Biological Similarities between Ageing and Obesity

Ageing and obesity are major topics in biomedical studies, mainly because both represent risk factors for numerous diseases and health conditions [1]. The modern lifestyle and industrial development have increased obesity rates as well as the aged population percentage worldwide. Obesity is specifically increasing among the elderly [2,3], which contributes to sarcopenic obesity, a chronic, age-related class of obesity [4,5]. These interactions between two important risk factors strengthen the need to further deepen our biological and clinical understanding of the interrelation and correlations between ageing and obesity. Such mechanistic elucidation would allow to develop the medical care including geriatrics and obesity management, among other chronic diseases. Within this piece of writing, we aim to elucidate selected links between ageing and obesity through different illustrations starting from pathogenesis and molecular pathways towards epigenetics, supported by evidences from exercise being a therapeutic tool for both.

Obesity is defined as an abnormal accumulation of adiposity resulting from a disturbed energy balance in which energy intake is higher than energy expenditure [6] with a modified metabolic phenotype [7], complex neuroendocrine changes [8], and pathogenic implications [9]. Obesity has even been classified as a disease [10] and associated with health problems including impaired fertility [11,12], neurodegenerative disease [13], cognitive decline (in mid-life) [14], coronavirus disease 2019 (COVID-19) severity and resulting health problems [15–18], type 2 diabetes [19], cancer [20], cardiovascular diseases [21], pulmonary diseases [22], insulin resistance [23], atherosclerosis [24], mitochondrial dysfunction [25], dyslipidemia [26], liver disease [27], impaired immunity [28,29], and impaired regeneration [30]. Ageing, on the other hand, represents the progressive decline of the biological functions with time [31]. It also represents a risk factor for numerous diseases

and health conditions, many of which are similar to those associated with obesity. These include neurodegenerative disease [32], cognitive decline [33], COVID-19 severity [34], type 2 diabetes [35], skeletal muscle loss [36], cancer [37], cardiovascular disease [38], pulmonary disease [39], insulin resistance [40], atherosclerosis [41], mitochondrial dysfunction [42], dyslipidemia [43], liver disease [44], fertility alteration [45,46] immunity alteration [47], and declined regeneration [48].

Although the risks related to obesity are independent from ageing and those related to ageing are independent from obesity, such similarities between ageing and obesity as risk factors suggest common patterns and share underlying mechanisms of both ageing and obesity. Early epidemiologic data approved the prevalence of obesity increases by ageing, especially in women. Therefore, the ongoing step is to know more about how ageing and obesity could be related at the molecular level. Within this context, obesity and ageing have been described as sharing common pathways at the molecular and cellular levels. For instance, in both, we have increased inflammation [49,50], free radicals, and oxidative stress [51,52] as well as microbiota changes [53,54]. In addition, healthy diet and physical activity are prescribed to manage obesity [55,56] and also optimize healthy ageing [57,58]. While the main goal of prescribing the physical activity in obesity is to increase the energy expenditure and, thus, reduce the adiposity and lose weight [59,60], in ageing, the physical activity aims mostly to improve muscular and metabolic performance [57,61,62]. Importantly, physical activity as a common therapy for both ageing and obesity has significant impacts on reducing the risk factors mediated by ageing and obesity and also improves numerous biomolecular markers and pathological profiles. As illustrations, physical activity improves and optimizes treatment/prevention or reduces the risk of metabolic disorders [63], cancer [64], cardiovascular disease [65–67], immune functions [68], insulin resistance [69], oxidative stress [70], liver disease [71], regeneration [72,73], pulmonary disease [74,75], atherosclerosis [76], and mitochondrial remodeling [77]. These evidences add up on those of functional genomics [78–81] as illustrated by the secreted protein acidic and rich in cysteine (SPARC). Indeed, SPARC expression changes during obesity [82] and with ageing [83] and *Sparc*/SPARC represents an exercise-induced gene upon which exercise-induced muscle phenotype changes would depend [84,85]. In addition, SPARC is involved in diverse biological activities [86] related to those described above in the context of obesity, ageing, and exercise. These include metabolic and homeostatic properties [87], inflammation [88], cancer [89], regeneration [90], and metabolism [91]. This exercise-induced key myokine with obesity and age-related expression patterns further points to molecular links between obesity and ageing.

2. Epigenetics: An Additional Link between Ageing and Obesity

Furthermore, epigenetics studies provide additional evidences of similar patterns shared by obesity and ageing. Therefore, epigenetics represents a field worth exploring to reveal further links between obesity and ageing. This is reflected by the changes such as histone modification, DNA methylation, noncoding RNAs, and chromatin remodeling that have been associated with both ageing [31,92–97] and obesity [98–103]. These changes can follow diverse patterns. For instance, region-specific DNA hypermethylation [104] and proliferation-dependent alterations of the DNA methylation [105] have been reported in ageing during which we talk about epigenetic clocks [106]. The possible use of DNA-methylation-based measures as a tool to evaluate the accelerated biological ageing [107–110] represents a potential application of the DNA methylation age (DNAMAge), which would contribute to several diseases such as obesity. Similarly, obesity-related DNA methylation can be site-specific [111] and with specific methylation signatures [112]. Other related features such as telomere attrition are also shared between ageing [31] and obesity [113,114].

Importantly, exercise—prescribed for both elderly and obese patients—has impacts on the epigenetics patterns related to both ageing and obesity including DNA methylation [115], histone modification [116], chromatin modifications [117], and noncoding RNAs [118]. These exercise-related properties suggest that epigenetics pathways are

among the mechanisms via which exercise induces its benefits—as it has been shown, for instance, for exercise-mediated heart protection [119]. They further support targeting epigenetic pathways as a therapy [120,121] as well; potentially, to treat obesity and improve ageing. These observations also suggest correlations between epigenetics changes and obesity/ageing-related pathologic phenotypes. In addition, these molecular and clinical evidences, from genetics to epigenetics and pathogenesis, further present obesity as a risk factor for ageing and, at the same time, highlight ageing as a risk factor for obesity [1]. This would explain why losing weight “rejuvenates”. Moreover, dietary restriction (that has both antiageing and antiobesity effects) also impacts epigenetics towards significant health benefits [122,123] bringing an additional correlation between ageing and obesity.

3. Perspectives

These introduced concepts would have important applications in the medical fields, especially that both ageing and obesity are among what medically characterize the epidemiological and pathological profiles of most modern societies. Although a healthy ageing is the optimum target of geriatrics, we have limited options to manage ageing (irreversible time effects). However, obesity, on the other hand, has realistically more management options since it remains relatively reversible. Therefore, managing obesity toward healthy ageing remains more practical than targeting healthy ageing to manage obesity. It is worth noting, however, that treating obesity would optimize ageing and healthy ageing would decrease obesity risk. Nevertheless, the key approach remains to target a healthy lifestyle including exercise, diet, sleeping, and psychological well-being to manage obesity, optimize healthy ageing, and control most diseases’ risk factors.

We would like to introduce a new concept via which there is a potential to combine the age-related and the obesity-related epigenetics measures to obtain a full evaluation of how deep both the age and obesity worsen the other as well as the various diseases and risk factors for which either ageing or obesity represent a risk factor. The need to actualize this idea nowadays comes from the urgent epidemiological situations related to ageing and obesity in the modern societies both in developed and in developing countries. To expand this vision, the advances and added value of this work is that it puts epigenetics along with pathological phenotype, molecular patterns, and lifestyle impacts as a set that regroups the elements shared between obesity and ageing (Figure 1). Such approaches would allow for optimizing therapies and lifestyle management choices.

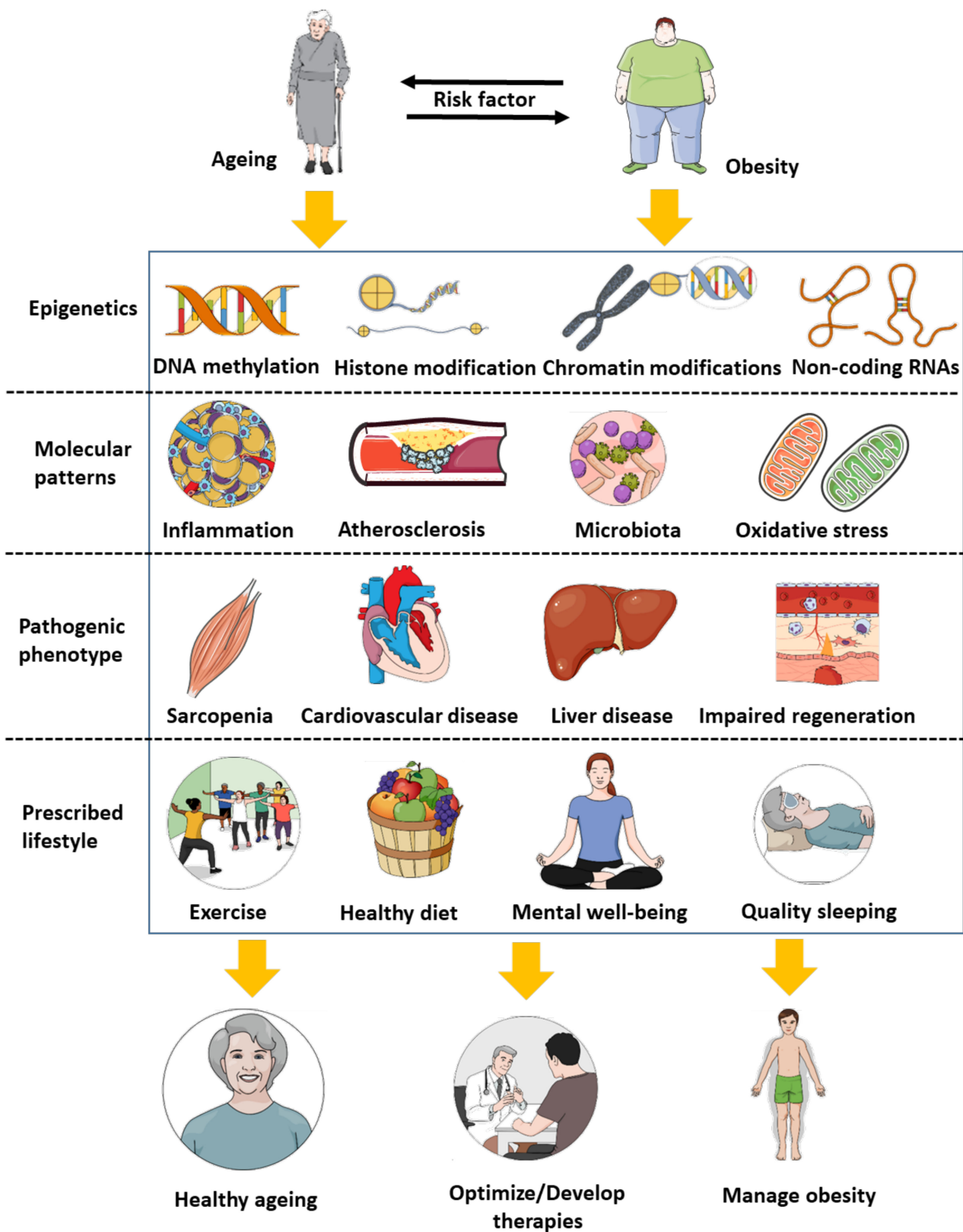


Figure 1. Examples of ageing and obesity shared patterns. Both ageing and obesity represent a risk factor for each other. Elucidating the patterns shared between ageing and obesity, from epigenetics to molecular pathogenesis, would allow to both optimize healthy ageing and manage obesity.

Author Contributions: A.G. designed the manuscript structure and wrote it. A.G., M.Y., and J.S.-A. discussed the content and exchanged ideas and suggestions (concepts to add, the figure, references selection, etc.) throughout the writing process, edited, and critically revised the paper. J.S.-A. gave the final approval for the version to be published. All authors have read and agreed to the published version of the manuscript.

Funding: This work received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: Abdelaziz Ghanemi received a scholarship under the Merit Scholarship Program for foreign students from the Ministry of Education and Higher Education of Quebec, Canada. The Fonds de recherche du Québec—Nature et technologies (FRQNT) is responsible for managing the program (Bourses d'excellence pour étudiants étrangers du Ministère de l'Éducation et de l'Enseignement supérieur du Québec, Le Fonds de recherche du Québec—Nature et technologies (FRQNT) est responsable de la gestion du programme). Abdelaziz Ghanemi is the received the scholarship « Bourse Tremplin -Stage en milieu de pratique» (Internship scholarship) from the Fonds de recherche du Québec-Santé (FRQS), Quebec, Canada. Figure 1 was created using images from <https://mindthegraph.com/> and <http://smart.servier.com>. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (accessed on 26 October 2021).

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Jura, M.; Kozak, L.P. Obesity and related consequences to ageing. *Age* **2016**, *38*, 23. [[CrossRef](#)] [[PubMed](#)]
2. Han, T.S.; Tajar, A.; Lean, M.E. Obesity and weight management in the elderly. *Br. Med. Bull.* **2011**, *97*, 169–196. [[CrossRef](#)]
3. Han, T.S.; Wu, F.C.; Lean, M.E. Obesity and weight management in the elderly: A focus on men. *Best Pract. Res. Clin. Endocrinol. Metab.* **2013**, *27*, 509–525. [[CrossRef](#)] [[PubMed](#)]
4. Batsis, J.A.; Villareal, D.T. Sarcopenic obesity in older adults: Aetiology, epidemiology and treatment strategies. *Nat. Rev. Endocrinol.* **2018**, *14*, 513–537. [[CrossRef](#)]
5. Polyzos, S.A.; Margioris, A.N. Sarcopenic obesity. *Hormones* **2018**, *17*, 321–331. [[CrossRef](#)] [[PubMed](#)]
6. Ghanemi, A.; Yoshioka, M.; St-Amand, J. Broken Energy Homeostasis and Obesity Pathogenesis: The Surrounding Concepts. *J. Clin. Med.* **2018**, *7*, 453. [[CrossRef](#)] [[PubMed](#)]
7. Goossens, G.H. The Metabolic Phenotype in Obesity: Fat Mass, Body Fat Distribution, and Adipose Tissue Function. *Obes. Facts* **2017**, *10*, 207–215. [[CrossRef](#)] [[PubMed](#)]
8. Ghanemi, A.; Yoshioka, M.; St-Amand, J. Obesity as a Neuroendocrine Reprogramming. *Medicina* **2021**, *57*, 66. [[CrossRef](#)]
9. Ghanemi, A.; Yoshioka, M.; St-Amand, J. Obese Animals as Models for Numerous Diseases: Advantages and Applications. *Medicina* **2021**, *57*, 999. [[CrossRef](#)] [[PubMed](#)]
10. Ghanemi, A.; St-Amand, J. Redefining obesity toward classifying as a disease. *Eur. J. Intern. Med.* **2018**, *55*, 20–22. [[CrossRef](#)] [[PubMed](#)]
11. Škurla, M.; Rybář, R. Obesity and reduced fertility of men. *Ceska Gynecol.* **2018**, *83*, 212–217. [[PubMed](#)]
12. Best, D.; Bhattacharya, S. Obesity and fertility. *Horm. Mol. Biol. Clin. Investig.* **2015**, *24*, 5–10. [[CrossRef](#)]
13. Saad, M.J.; Santos, A.; Prada, P.O. Linking Gut Microbiota and Inflammation to Obesity and Insulin Resistance. *Physiology* **2016**, *31*, 283–293. [[CrossRef](#)] [[PubMed](#)]
14. Dye, L.; Boyle, N.B.; Champ, C.; Lawton, C. The relationship between obesity and cognitive health and decline. *Proc. Nutr. Soc.* **2017**, *76*, 443–454. [[CrossRef](#)]
15. Petrakis, D.; Margină, D.; Tsarouhas, K.; Tekos, F.; Stan, M.; Nikitovic, D.; Kouretas, D.; Spandidos, D.A.; Tsatsakis, A. Obesity—A risk factor for increased COVID-19 prevalence, severity and lethality (Review). *Mol. Med. Rep.* **2020**, *22*, 9–19. [[CrossRef](#)] [[PubMed](#)]
16. Ghanemi, A.; Yoshioka, M.; St-Amand, J. Will an obesity pandemic replace the coronavirus disease-2019 (COVID-19) pandemic? *Med. Hypotheses* **2020**, *144*, 110042. [[CrossRef](#)]
17. Ghanemi, A.; Yoshioka, M.; St-Amand, J. Coronavirus Disease 2019 (COVID-19) Crisis: Losing Our Immunity When We Need It the Most. *Biology* **2021**, *10*, 545. [[CrossRef](#)] [[PubMed](#)]
18. Ghanemi, A.; Yoshioka, M.; St-Amand, J. Post-Coronavirus Disease-2019 (COVID-19): Toward a Severe Multi-Level Health Crisis? *Med. Sci.* **2021**, *9*, 68. [[CrossRef](#)]
19. Rubio-Almanza, M.; Cámara-Gómez, R.; Merino-Torres, J.F. Obesity and type 2 diabetes: Also linked in therapeutic options. *Endocrinol. Diabetes Nutr.* **2019**, *66*, 140–149. [[CrossRef](#)] [[PubMed](#)]

20. Avgerinos, K.I.; Spyrou, N.; Mantzoros, C.S.; Dalamaga, M. Obesity and cancer risk: Emerging biological mechanisms and perspectives. *Metabolism* **2019**, *92*, 121–135. [[CrossRef](#)]
21. Koliaki, C.; Liatis, S.; Kokkinos, A. Obesity and cardiovascular disease: Revisiting an old relationship. *Metabolism* **2019**, *92*, 98–107. [[CrossRef](#)] [[PubMed](#)]
22. Dixon, A.E.; Peters, U. The effect of obesity on lung function. *Expert Rev. Respir. Med.* **2018**, *12*, 755–767. [[CrossRef](#)]
23. Barazzoni, R.; Gortan Cappellari, G.; Ragni, M.; Nisoli, E. Insulin resistance in obesity: An overview of fundamental alterations. *Eat Weight Disord.* **2018**, *23*, 149–157. [[CrossRef](#)] [[PubMed](#)]
24. Csige, I.; Ujvárosy, D.; Szabó, Z.; Lőrincz, I.; Paragh, G.; Harangi, M.; Somodi, S. The Impact of Obesity on the Cardiovascular System. *J. Diabetes Res.* **2018**, *2018*, 3407306. [[CrossRef](#)] [[PubMed](#)]
25. De Mello, A.H.; Costa, A.B.; Engel, J.D.G.; Rezin, G.T. Mitochondrial dysfunction in obesity. *Life Sci.* **2018**, *192*, 26–32. [[CrossRef](#)]
26. Vekic, J.; Zeljkovic, A.; Stefanovic, A.; Jelic-Ivanovic, Z.; Spasojevic-Kalimanovska, V. Obesity and dyslipidemia. *Metabolism* **2019**, *92*, 71–81. [[CrossRef](#)]
27. Polyzos, S.A.; Kountouras, J.; Mantzoros, C.S. Obesity and nonalcoholic fatty liver disease: From pathophysiology to therapeutics. *Metabolism* **2019**, *92*, 82–97. [[CrossRef](#)] [[PubMed](#)]
28. Andersen, C.J.; Murphy, K.E.; Fernandez, M.L. Impact of Obesity and Metabolic Syndrome on Immunity. *Adv. Nutr.* **2016**, *7*, 66–75. [[CrossRef](#)]
29. Ghanemi, A.; Yoshioka, M.; St-Amand, J. Impact of Adiposity and Fat Distribution, Rather Than Obesity, on Antibodies as an Illustration of Weight-Loss-Independent Exercise Benefits. *Medicines* **2021**, *8*, 57. [[CrossRef](#)] [[PubMed](#)]
30. Ghanemi, A.; Yoshioka, M.; St-Amand, J. Regeneration during Obesity: An Impaired Homeostasis. *Animals* **2020**, *10*, 2344. [[CrossRef](#)] [[PubMed](#)]
31. López-Otín, C.; Blasco, M.A.; Partridge, L.; Serrano, M.; Kroemer, G. The hallmarks of aging. *Cell* **2013**, *153*, 1194–1217. [[CrossRef](#)] [[PubMed](#)]
32. Hou, Y.; Dan, X.; Babbar, M.; Wei, Y.; Hasselbalch, S.G.; Croteau, D.L.; Bohr, V.A. Ageing as a risk factor for neurodegenerative disease. *Nat. Rev. Neurol.* **2019**, *15*, 565–581. [[CrossRef](#)] [[PubMed](#)]
33. Bramorska, A.; Zarzycka, W.; Podolecka, W.; Kuc, K.; Brzezicka, A. Age-Related Cognitive Decline May Be Moderated by Frequency of Specific Food Products Consumption. *Nutrients* **2021**, *13*, 2504. [[CrossRef](#)] [[PubMed](#)]
34. Gallo Marin, B.; Aghagoli, G.; Lavine, K.; Yang, L.; Siff, E.J.; Chiang, S.S.; Salazar-Mather, T.P.; Dumenco, L.; Savaria, M.C.; Aung, S.N.; et al. Predictors of COVID-19 severity: A literature review. *Rev. Med. Virol.* **2021**, *31*, 1–10. [[CrossRef](#)]
35. Al-Sofiani, M.E.; Ganji, S.S.; Kalyani, R.R. Body composition changes in diabetes and aging. *J. Diabetes Complicat.* **2019**, *33*, 451–459. [[CrossRef](#)] [[PubMed](#)]
36. Park, S.W.; Goodpaster, B.H.; Lee, J.S.; Kuller, L.H.; Boudreau, R.; de Rekeneire, N.; Harris, T.B.; Kritchevsky, S.; Tylavsky, F.A.; Nevitt, M.; et al. Excessive loss of skeletal muscle mass in older adults with type 2 diabetes. *Diabetes Care* **2009**, *32*, 1993–1997. [[CrossRef](#)]
37. Fane, M.; Weeraratna, A.T. How the ageing microenvironment influences tumour progression. *Nat. Rev. Cancer* **2020**, *20*, 89–106. [[CrossRef](#)]
38. Costantino, S.; Paneni, F.; Cosentino, F. Ageing, metabolism and cardiovascular disease. *J. Physiol.* **2016**, *594*, 2061–2073. [[CrossRef](#)] [[PubMed](#)]
39. Barnes, P.J. Pulmonary Diseases and Ageing. *Subcell. Biochem.* **2019**, *91*, 45–74. [[PubMed](#)]
40. Consitt, L.A.; Dudley, C.; Saxena, G. Impact of Endurance and Resistance Training on Skeletal Muscle Glucose Metabolism in Older Adults. *Nutrients* **2019**, *11*, 2636. [[CrossRef](#)]
41. Tyrrell, D.J.; Goldstein, D.R. Ageing and atherosclerosis: Vascular intrinsic and extrinsic factors and potential role of IL-6. *Nat. Rev. Cardiol.* **2021**, *18*, 58–68. [[CrossRef](#)] [[PubMed](#)]
42. Tyrrell, D.J.; Blin, M.G.; Song, J.; Wood, S.C.; Zhang, M.; Beard, D.A.; Goldstein, D.R. Age-Associated Mitochondrial Dysfunction Accelerates Atherogenesis. *Circ. Res.* **2020**, *126*, 298–314. [[CrossRef](#)]
43. Liu, H.H.; Li, J.J. Aging and dyslipidemia: A review of potential mechanisms. *Ageing Res. Rev.* **2015**, *19*, 43–52. [[CrossRef](#)] [[PubMed](#)]
44. Stahl, E.C.; Haschak, M.J.; Popovic, B.; Brown, B.N. Macrophages in the Aging Liver and Age-Related Liver Disease. *Front. Immunol.* **2018**, *9*, 2795. [[CrossRef](#)] [[PubMed](#)]
45. Almeida, S.; Rato, L.; Sousa, M.; Alves, M.G.; Oliveira, P.F. Fertility and Sperm Quality in the Aging Male. *Curr. Pharm. Des.* **2017**, *23*, 4429–4437. [[CrossRef](#)]
46. American College of Obstetricians and Gynecologists Committee on Gynecologic Practice and Practice Committee. Female age-related fertility decline. Committee Opinion No. 589. *Fertil. Steril.* **2014**, *101*, 633–634. [[CrossRef](#)]
47. Sadighi Akha, A.A. Aging and the immune system: An overview. *J. Immunol. Methods* **2018**, *463*, 21–26. [[CrossRef](#)]
48. Sousounis, K.; Baddour, J.A.; Tsonis, P.A. Aging and regeneration in vertebrates. *Curr. Top Dev. Biol.* **2014**, *108*, 217–246.
49. Cox, A.J.; West, N.P.; Cripps, A.W. Obesity, inflammation, and the gut microbiota. *Lancet Diabetes Endocrinol.* **2015**, *3*, 207–215. [[CrossRef](#)]
50. Sendama, W. The effect of ageing on the resolution of inflammation. *Ageing Res. Rev.* **2020**, *57*, 101000. [[CrossRef](#)]
51. Pomatto, L.C.D.; Davies, K.J.A. Adaptive homeostasis and the free radical theory of ageing. *Free Radic. Biol Med.* **2018**, *124*, 420–430. [[CrossRef](#)] [[PubMed](#)]

52. Rani, V.; Deep, G.; Singh, R.K.; Palle, K.; Yadav, U.C. Oxidative stress and metabolic disorders: Pathogenesis and therapeutic strategies. *Life Sci.* **2016**, *148*, 183–193. [[CrossRef](#)] [[PubMed](#)]
53. Torres-Fuentes, C.; Schellekens, H.; Dinan, T.G.; Cryan, J.F. The microbiota-gut-brain axis in obesity. *Lancet Gastroenterol. Hepatol.* **2017**, *2*, 747–756. [[CrossRef](#)]
54. Dinan, T.G.; Cryan, J.F. Gut instincts: Microbiota as a key regulator of brain development, ageing and neurodegeneration. *J. Physiol.* **2017**, *595*, 489–503. [[CrossRef](#)] [[PubMed](#)]
55. Fock, K.M.; Khoo, J. Diet and exercise in management of obesity and overweight. *J. Gastroenterol. Hepatol.* **2013**, *28* (Suppl. S4), 59–63. [[CrossRef](#)]
56. Swift, D.L.; McGee, J.E.; Earnest, C.P.; Carlisle, E.; Nygard, M.; Johannsen, N.M. The Effects of Exercise and Physical Activity on Weight Loss and Maintenance. *Prog. Cardiovasc. Dis.* **2018**, *61*, 206–213. [[CrossRef](#)]
57. Papaioannou, K.G.; Nilsson, A.; Nilsson, L.M.; Kadi, F. Healthy Eating Is Associated with Sarcopenia Risk in Physically Active Older Adults. *Nutrients* **2021**, *13*, 2813. [[CrossRef](#)]
58. Mora, J.C.; Valencia, W.M. Exercise and Older Adults. *Clin. Geriatr. Med.* **2018**, *34*, 145–162. [[CrossRef](#)] [[PubMed](#)]
59. Stoner, L.; Beets, M.W.; Brazendale, K.; Moore, J.B.; Weaver, R.G. Exercise Dose and Weight Loss in Adolescents with Overweight-Obesity: A Meta-Regression. *Sports Med.* **2019**, *49*, 83–94. [[CrossRef](#)] [[PubMed](#)]
60. Swift, D.L.; Johannsen, N.M.; Lavie, C.J.; Earnest, C.P.; Church, T.S. The role of exercise and physical activity in weight loss and maintenance. *Prog. Cardiovasc. Dis.* **2014**, *56*, 441–447. [[CrossRef](#)] [[PubMed](#)]
61. Elia, M. Obesity in the elderly. *Obes. Res.* **2001**, *9* (Suppl. S4), 244s–248s. [[CrossRef](#)]
62. Fleg, J.L. Aerobic exercise in the elderly: A key to successful aging. *Discov. Med.* **2012**, *13*, 223–228. [[PubMed](#)]
63. Ghanemi, A.; St-Amand, J. Interleukin-6 as a “metabolic hormone”. *Cytokine* **2018**, *112*, 132–136. [[CrossRef](#)] [[PubMed](#)]
64. Idorn, M.; Thor Straten, P. Exercise and cancer: From “healthy” to “therapeutic”? *Cancer Immunol. Immunother.* **2017**, *66*, 667–671. [[CrossRef](#)] [[PubMed](#)]
65. Cattadori, G.; Segurini, C.; Picozzi, A.; Padeletti, L.; Anzà, C. Exercise and heart failure: An update. *ESC Heart Fail.* **2018**, *5*, 222–232. [[CrossRef](#)]
66. Fiuza-Luces, C.; Santos-Lozano, A.; Joyner, M.; Carrera-Bastos, P.; Picazo, O.; Zugaza, J.L.; Izquierdo, M.; Ruilope, L.M.; Lucia, A. Exercise benefits in cardiovascular disease: Beyond attenuation of traditional risk factors. *Nat. Rev. Cardiol.* **2018**, *15*, 731–743. [[CrossRef](#)]
67. Hansen, D.; Niebauer, J.; Cornelissen, V.; Barna, O.; Neunhäuserer, D.; Stettler, C.; Tonoli, C.; Greco, E.; Fagard, R.; Coninx, K.; et al. Exercise Prescription in Patients with Different Combinations of Cardiovascular Disease Risk Factors: A Consensus Statement from the EXPERT Working Group. *Sports Med.* **2018**, *48*, 1781–1797. [[CrossRef](#)]
68. Wang, J.; Liu, S.; Li, G.; Xiao, J. Exercise Regulates the Immune System. *Adv. Exp. Med. Biol.* **2020**, *1228*, 395–408. [[PubMed](#)]
69. Whillier, S. Exercise and Insulin Resistance. *Adv. Exp. Med. Biol.* **2020**, *1228*, 137–150.
70. De Sousa, C.V.; Sales, M.M.; Rosa, T.S.; Lewis, J.E.; de Andrade, R.V.; Simões, H.G. The Antioxidant Effect of Exercise: A Systematic Review and Meta-Analysis. *Sports Med.* **2017**, *47*, 277–293. [[CrossRef](#)]
71. Van der Windt, D.J.; Sud, V.; Zhang, H.; Tsung, A.; Huang, H. The Effects of Physical Exercise on Fatty Liver Disease. *Gene Expr.* **2018**, *18*, 89–101. [[CrossRef](#)] [[PubMed](#)]
72. Saito, Y.; Chikenji, T.S.; Matsumura, T.; Nakano, M.; Fujimiya, M. Exercise enhances skeletal muscle regeneration by promoting senescence in fibro-adipogenic progenitors. *Nat. Commun.* **2020**, *11*, 889. [[CrossRef](#)] [[PubMed](#)]
73. Schüttler, D.; Clauss, S.; Weckbach, L.T.; Brunner, S. Molecular Mechanisms of Cardiac Remodeling and Regeneration in Physical Exercise. *Cells* **2019**, *8*, 1128. [[CrossRef](#)]
74. Paneroni, M.; Simonelli, C.; Vitacca, M.; Ambrosino, N. Aerobic Exercise Training in Very Severe Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis. *Am. J. Phys. Med. Rehabil.* **2017**, *96*, 541–548. [[CrossRef](#)]
75. Nolan, C.M.; Rochester, C.L. Exercise Training Modalities for People with Chronic Obstructive Pulmonary Disease. *COPD* **2019**, *16*, 378–389. [[CrossRef](#)] [[PubMed](#)]
76. Yang, J.; Cao, R.Y.; Gao, R.; Mi, Q.; Dai, Q.; Zhu, F. Physical Exercise Is a Potential “Medicine” for Atherosclerosis. *Adv. Exp. Med. Biol.* **2017**, *999*, 269–286.
77. Gan, Z.; Fu, T.; Kelly, D.P.; Vega, R.B. Skeletal muscle mitochondrial remodeling in exercise and diseases. *Cell Res.* **2018**, *28*, 969–980. [[CrossRef](#)]
78. Ghanemi, A.; Melouane, A.; Yoshioka, M.; St-Amand, J. Exercise and High-Fat Diet in Obesity: Functional Genomics Perspectives of Two Energy Homeostasis Pillars. *Genes* **2020**, *11*, 875. [[CrossRef](#)]
79. Melouane, A.; Ghanemi, A.; Yoshioka, M.; St-Amand, J. Functional genomics applications and therapeutic implications in sarcopenia. *Mutat. Res. Rev. Mutat. Res.* **2019**, *781*, 175–185. [[CrossRef](#)]
80. Melouane, A.; Ghanemi, A.; Aubé, S.; Yoshioka, M.; St-Amand, J. Differential gene expression analysis in ageing muscle and drug discovery perspectives. *Ageing Res. Rev.* **2018**, *41*, 53–63. [[CrossRef](#)]
81. Mucunguzi, O.; Melouane, A.; Ghanemi, A.; Yoshioka, M.; Boivin, A.; Calvo, E.L.; St-Amand, J. Identification of the principal transcriptional regulators for low-fat and high-fat meal responsive genes in small intestine. *Nutr. Metab.* **2017**, *14*, 66. [[CrossRef](#)]
82. Atorrasagasti, C.; Onorato, A.; Gimeno, M.L.; Andreone, L.; Garcia, M.; Malvicini, M.; Fiore, E.; Bayo, J.; Perone, M.J.; Mazzolini, G.D. SPARC is required for the maintenance of glucose homeostasis and insulin secretion in mice. *Clin. Sci.* **2019**, *133*, 351–365. [[CrossRef](#)]

83. Kwon, J.H.; Moon, K.M.; Min, K.W. Exercise-Induced Myokines can Explain the Importance of Physical Activity in the Elderly: An Overview. *Healthcare* **2020**, *8*, 378. [[CrossRef](#)] [[PubMed](#)]
84. Ghanemi, A.; Melouane, A.; Yoshioka, M.; St-Amand, J. Exercise Training of Secreted Protein Acidic and Rich in Cysteine (Sparc) KO Mice Suggests That Exercise-Induced Muscle Phenotype Changes Are SPARC-Dependent. *Appl. Sci.* **2020**, *10*, 9108. [[CrossRef](#)]
85. Ghanemi, A.; Yoshioka, M.; St-Amand, J. Measuring Exercise-Induced Secreted Protein Acidic and Rich in Cysteine Expression as a Molecular Tool to Optimize Personalized Medicine. *Genes* **2021**, *12*, 1832. [[CrossRef](#)] [[PubMed](#)]
86. Ghanemi, A.; Yoshioka, M.; St-Amand, J. Secreted Protein Acidic and Rich in Cysteine as a Molecular Physiological and Pathological Biomarker. *Biomolecules* **2021**, *11*, 1689. [[CrossRef](#)]
87. Ghanemi, A.; Yoshioka, M.; St-Amand, J. Secreted Protein Acidic and Rich in Cysteine: Metabolic and Homeostatic Properties beyond the Extracellular Matrix Structure. *Appl. Sci.* **2020**, *10*, 2388. [[CrossRef](#)]
88. Ghanemi, A.; Yoshioka, M.; St-Amand, J. Secreted protein acidic and rich in cysteine and inflammation: Another homeostatic property? *Cytokine* **2020**, *133*, 155179. [[CrossRef](#)] [[PubMed](#)]
89. Ghanemi, A.; Yoshioka, M.; St-Amand, J. Secreted protein acidic and rich in cysteine and cancer: A homeostatic hormone? *Cytokine* **2020**, *127*, 154996. [[CrossRef](#)]
90. Ghanemi, A.; Yoshioka, M.; St-Amand, J. Secreted Protein Acidic and Rich in Cysteine as a Regeneration Factor: Beyond the Tissue Repair. *Life* **2021**, *11*, 38. [[CrossRef](#)]
91. Ghanemi, A.; Melouane, A.; Yoshioka, M.; St-Amand, J. Secreted protein acidic and rich in cysteine and bioenergetics: Extracellular matrix, adipocytes remodeling and skeletal muscle metabolism. *Int. J. Biochem. Cell Biol.* **2019**, *117*, 105627. [[CrossRef](#)]
92. Morgan, A.E.; Davies, T.J.; Mc Auley, M.T. The role of DNA methylation in ageing and cancer. *Proc. Nutr. Soc.* **2018**, *77*, 412–422. [[CrossRef](#)] [[PubMed](#)]
93. Zhang, W.; Qu, J.; Liu, G.H.; Belmonte, J.C.I. The ageing epigenome and its rejuvenation. *Nat. Rev. Mol. Cell Biol.* **2020**, *21*, 137–150. [[CrossRef](#)] [[PubMed](#)]
94. Covarrubias, A.J.; Perrone, R.; Grozio, A.; Verdin, E. NAD(+) metabolism and its roles in cellular processes during ageing. *Nat. Rev. Mol. Cell Biol.* **2021**, *22*, 119–141. [[CrossRef](#)] [[PubMed](#)]
95. Booth, L.N.; Brunet, A. The Aging Epigenome. *Mol. Cell.* **2016**, *62*, 728–744. [[CrossRef](#)]
96. Thum, T. Non-coding RNAs in ageing. *Ageing Res. Rev.* **2014**, *17*, 1–2. [[CrossRef](#)]
97. Gupta, S.K.; Piccoli, M.T.; Thum, T. Non-coding RNAs in cardiovascular ageing. *Ageing Res. Rev.* **2014**, *17*, 79–85. [[CrossRef](#)]
98. Samblas, M.; Milagro, F.I.; Martínez, A. DNA methylation markers in obesity, metabolic syndrome, and weight loss. *Epigenetics* **2019**, *14*, 421–444. [[CrossRef](#)]
99. Ling, C.; Rönn, T. Epigenetics in Human Obesity and Type 2 Diabetes. *Cell Metab.* **2019**, *29*, 1028–1044. [[CrossRef](#)]
100. Horikoshi, M.; Beaumont, R.N.; Day, F.R.; Warrington, N.M.; Kooijman, M.N.; Fernandez-Tajés, J.; Feenstra, B.; van Zuydam, N.R.; Gaulton, K.J.; Grarup, N.; et al. Genome-wide associations for birth weight and correlations with adult disease. *Nature* **2016**, *538*, 248–252. [[CrossRef](#)]
101. Eeckhoutte, J.; Oger, F.; Staels, B.; Lefebvre, P. Coordinated Regulation of PPAR γ Expression and Activity through Control of Chromatin Structure in Adipogenesis and Obesity. *PPAR Res.* **2012**, *2012*, 164140. [[CrossRef](#)]
102. Shi, Y.; Qu, J.; Gai, L.; Yuan, D.; Yuan, C. Long Non-coding RNAs in Metabolic and Inflammatory Pathways in Obesity. *Curr. Pharm. Des.* **2020**, *26*, 3317–3325. [[CrossRef](#)] [[PubMed](#)]
103. Ouni, M.; Schürmann, A. Epigenetic contribution to obesity. *Mamm. Genome.* **2020**, *31*, 134–145. [[CrossRef](#)]
104. Jung, M.; Pfeifer, G.P. Aging and DNA methylation. *BMC Biol.* **2015**, *13*, 7. [[CrossRef](#)] [[PubMed](#)]
105. Berman, I.; Bock, C.; Garrison, B.S.; Smith, Z.D.; Gu, H.; Meissner, A.; Rossi, D.J. Proliferation-dependent alterations of the DNA methylation landscape underlie hematopoietic stem cell aging. *Cell Stem. Cell* **2013**, *12*, 413–425. [[CrossRef](#)]
106. Unnikrishnan, A.; Freeman, W.M.; Jackson, J.; Wren, J.D.; Porter, H.; Richardson, A. The role of DNA methylation in epigenetics of aging. *Pharmacol. Ther.* **2019**, *195*, 172–185. [[CrossRef](#)] [[PubMed](#)]
107. Sibbett, R.A.; Altschul, D.M.; Marioni, R.E.; Deary, I.J.; Starr, J.M.; Russ, T.C. DNA methylation-based measures of accelerated biological ageing and the risk of dementia in the oldest-old: A study of the Lothian Birth Cohort 1921. *BMC Psychiatry* **2020**, *20*, 91. [[CrossRef](#)]
108. Matías-García, P.R.; Ward-Caviness, C.K.; Raffield, L.M.; Gao, X.; Zhang, Y.; Wilson, R.; Gào, X.; Nano, J.; Bostom, A.; Colicino, E.; et al. DNAm-based signatures of accelerated aging and mortality in blood are associated with low renal function. *Clin. Epigenetics* **2021**, *13*, 121. [[CrossRef](#)]
109. Ambatipudi, S.; Horvath, S.; Perrier, F.; Cuenin, C.; Hernandez-Vargas, H.; Le Calvez-Kelm, F.; Durand, G.; Byrnes, G.; Ferrari, P.; Bouaoun, L.; et al. DNA methylome analysis identifies accelerated epigenetic ageing associated with postmenopausal breast cancer susceptibility. *Eur. J. Cancer* **2017**, *75*, 299–307. [[CrossRef](#)]
110. Peng, C.; Cardenas, A.; Rifas-Shiman, S.L.; Hivert, M.F.; Gold, D.R.; Platts-Mills, T.A.; Lin, X.; Oken, E.; Avila, L.; Celedón, J.C.; et al. Epigenetic age acceleration is associated with allergy and asthma in children in Project Viva. *J. Allergy Clin. Immunol.* **2019**, *143*, 2263–2270.e2214. [[CrossRef](#)]
111. Van Dijk, S.J.; Molloy, P.L.; Varinli, H.; Morrison, J.L.; Muhlhausler, B.S. Epigenetics and human obesity. *Int. J. Obes.* **2015**, *39*, 85–97. [[CrossRef](#)] [[PubMed](#)]

112. Ahrens, M.; Ammerpohl, O.; von Schönfels, W.; Kolarova, J.; Bens, S.; Itzel, T.; Teufel, A.; Herrmann, A.; Brosch, M.; Hinrichsen, H.; et al. DNA methylation analysis in nonalcoholic fatty liver disease suggests distinct disease-specific and remodeling signatures after bariatric surgery. *Cell Metab.* **2013**, *18*, 296–302. [[CrossRef](#)] [[PubMed](#)]
113. Zhou, Y.; Hambly, B.D.; McLachlan, C.S. FTO associations with obesity and telomere length. *J. Biomed. Sci.* **2017**, *24*, 65. [[CrossRef](#)] [[PubMed](#)]
114. Gurung, R.L.; Liu, S.; Liu, J.J.; Chan, S.M.; Moh, M.C.; Ang, K.; Tang, W.E.; Sum, C.F.; Tavintharan, S.; Lim, S.C. Ethnic disparities in relationships of obesity indices with telomere length in Asians with type 2 diabetes. *J. Diabetes* **2019**, *11*, 386–393. [[CrossRef](#)] [[PubMed](#)]
115. Voisin, S.; Eynon, N.; Yan, X.; Bishop, D.J. Exercise training and DNA methylation in humans. *Acta Physiol.* **2015**, *213*, 39–59. [[CrossRef](#)]
116. Fernandes, J.; Arida, R.M.; Gomez-Pinilla, F. Physical exercise as an epigenetic modulator of brain plasticity and cognition. *Neurosci. Biobehav. Rev.* **2017**, *80*, 443–456. [[CrossRef](#)]
117. Solagna, F.; Nogara, L.; Dyar, K.A.; Greulich, F.; Mir, A.A.; Türk, C.; Bock, T.; Geremia, A.; Baraldo, M.; Sartori, R.; et al. Exercise-dependent increases in protein synthesis are accompanied by chromatin modifications and increased MRTF-SRF signalling. *Acta Physiol.* **2020**, *230*, e13496. [[CrossRef](#)]
118. Bonilauri, B.; Dallagiovanna, B. Long Non-coding RNAs Are Differentially Expressed after Different Exercise Training Programs. *Front. Physiol.* **2020**, *11*, 567614. [[CrossRef](#)] [[PubMed](#)]
119. Zhang, Y.; He, N.; Feng, B.; Ye, H. Exercise Mediates Heart Protection via Non-coding RNAs. *Front. Cell Dev. Biol.* **2020**, *8*, 182. [[CrossRef](#)]
120. Dawson, M.A.; Kouzarides, T. Cancer epigenetics: From mechanism to therapy. *Cell* **2012**, *150*, 12–27. [[CrossRef](#)]
121. Miranda Furtado, C.L.; Dos Santos Luciano, M.C.; Silva Santos, R.D.; Furtado, G.P.; Moraes, M.O.; Pessoa, C. Epidrugs: Targeting epigenetic marks in cancer treatment. *Epigenetics* **2019**, *14*, 1164–1176. [[CrossRef](#)] [[PubMed](#)]
122. Yong-Quan Ng, G.; Yang-Wei Fann, D.; Jo, D.G.; Sobey, C.G.; Arumugam, T.V. Dietary Restriction and Epigenetics: Part I. *Cond. Med.* **2019**, *2*, 284–299. [[PubMed](#)]
123. Yong-Quan Ng, G.; Fann, D.Y.; Jo, D.G.; Sobey, C.G.; Arumugam, T.V. Epigenetic Regulation by Dietary Restriction: Part II. *Cond. Med.* **2019**, *2*, 300–310.