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Microbiome-Engineered Herbal Synbiotics for Regulating Ferroptosis and Mitochondrial Dysfunction in Age-Related Sarcopenia: A Mechanistic Review and Research Roadmap

[1]Mahalakshmi D, [2]Dr. Arvindkumar M. Chauhan, [3]Dr. Soundararajan K, [4]Supriya Awasthi, [5]Dr. Amol S. Dhawale, [6]Manisha Chandna,

[1]Assistant Professor, Shri Sathya Sai College of Nursing, Sri Balaji Vidyapeeth (Deemed to be University), Pondicherry, India
Mail ID: kalpanababu.pyr@gmail.com
Orcid id: 0009 -0006- 5062- 8631
[2]Professor, Faculty of Allied and Healthcare, Gokul Global University, Sidhpur, Gujarat, India.
dean.fac.parmed@gokuluniversity.ac.in
0000-0002-1595-7310
[3]Professor, Department of Orthopaedics, Vinayaka Mission's Kirupananda Variyar Medical College & Hospitals, Vinayaka Mission's Research Foundation (DU), Tamil Nadu, India.
Email ID: ksoundar25@gmail.com
ORCID ID: 0000-0001-7364-6732
[4]School of Allied Health Sciences, Noida International University, Uttar Pradesh, India.
supriya.awasthi@niu.edu.in
[5]Assistant Professor, Department of Orthopaedics, Krishna Institute of Medical Sciences, Krishna Vishwa Vidyapeeth "Deemed to be University, Taluka-Karad, Dist-Satara, Pin-415 539, Maharashtra, India
amol4loma@gmail.com
[6]Centre for Research Impact & Outcome, Chitkara University Institute of Engineering and Technology, Chitkara University, Rajpura, 140401, Punjab, India.
manisha.chandna.orp@chitkara.edu.in https://orcid.org/0009-0004-8300-9592

ABSTRACT: Sarcopenia – the age-associated progressive decline in muscle mass, strength, and functionality, predicted to impact over 200 million elderly people on the planet in four decades – has the following two converging cellular mechanisms of development: ferroptosis – an iron-mediated, lipid peroxidation-induced form of cell death recently shown to occur in sarcopenic mouse muscles by virtue of p53/SLC7A11/GPX4 pathway; and progressive mitochondrial malfunction, manifested by compromised mitochondrial biogenesis, defective mitophagy, and reduced oxidative activity. The two aforementioned cellular mechanisms are interrelated: dysfunctional mitochondria and mitochondrial fission lead to ferroptotic lipid peroxidation, and the latter results in further damage to the mitochondria – hence a vicious cycle mechanistically proven to exist in non-skeletal muscle tissue. In addition, there is quite a lot of evidence of the presence of gut-muscle axis, where certain microbial taxa of the gut, as well as short-chain fatty acids produced by them, determine muscle mass and functionality, whereas several plant-derived phytometabolites – curcumin, tannic acid, polydatin, and catechin

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among them – inhibit ferroptosis through the same p53/SLC7A11/GPX4 and Nrf2 pathway. The current review aims to hypothesise that engineered synbiotics (probiotics in combination with anti-ferroptosis herbal phytometabolites encapsulated in a plant-based matrix for targeted delivery to the colon, which is a technology that has already been validated in the case of another metabolic disease) would be capable of correcting age-related dysbiosis and delivering anti-ferroptosis and mitochondria protective phytometabolites to the skeletal muscles, thereby addressing both parts of the sarcopenia-driving mechanism via the single formulation. This strategy will be called microbiome-engineered herbal synbiotics. The review ends with a stepwise roadmap including in vitro, animal, and initial clinical translation stages. No novel experimental findings are provided; all the proposed links between mechanisms are formulated as hypotheses based on the existing evidence.

1. INTRODUCTION

Sarcopenia, recently defined as a standalone disease by the World Health Organization, and not a natural consequence of aging as was previously thought, will impact more than 200 million elderly individuals worldwide in the coming four decades, causing falls, fractures, loss of autonomy, and early deaths [1] [5]. In spite of the fact that there is so much about sarcopenia known today, its mechanisms of action have not been studied thoroughly (with descriptions limited to inflammatory processes, anabolic resistance, and oxidative stress), while specific molecular pathways amenable for treatment have not even been identified [9] [10]. There are two well-known pathways among those discovered recently (during the last five years): these are the ferroptosis pathway and the mitochondrial dysfunction one.

Ferroptosis is iron-mediated cell death resulting from uncontrollable lipid peroxidation, and it is distinct from apoptosis and necrosis. Ferroptosis was first defined in the context of cancer cells before being realized to be an important cause of tissue pathology [3]. One tissue in which ferroptosis is likely to be particularly significant is skeletal muscle since it contains 10-15% of total body iron and multiple independent studies have shown that there is an increase in the accumulation of iron within this tissue during aging, with the release of iron from storage playing a direct role in oxidative stress and inflammation [1] [7]. Causal evidence of ferroptosis comes from the observation made in a study using senescence-accelerated prone mouse 8 (SAMP8) model of accelerated aging, where the iron overload in sarcopenic muscles activates the p53-SLC7A11-GPX4 signaling pathway: p53 activation downregulates the cysteine/glutamate antiporter SLC7A11, which in turn reduces GPX4 activity, and this process can be rescued by treatment with a ferroptosis inhibitor ferrostatin-1 and iron chelator deferoxamine, thus confirming that the p53/SLC7A11/GPX4 signaling pathway plays a causal role in muscle ferroptosis in sarcopenia [4]. The study emphasizes the importance of secure medical data management to enable safe handling and sharing of clinical and patient data in microbiome and sarcopenia research [18].

Concurrently, it has long been known that mitochondrial dysfunction plays an integral part in the pathology of sarcopenia as characterized by mitochondrial biogenesis impairment, impaired oxidative phosphorylation coupling efficiency, and mitophagy – a selective removal via autophagy of defective mitochondria [2]. At the core of these processes lies the role of PGC-1α, a key regulator of mitochondrial biogenesis: aging results in elevated but apparently dysfunctional markers of mitophagy (increased LC3II, PINK1, Parkin, Fis-1) and decreased citrate synthase activity and cytochrome c oxidase content while overexpression of PGC-1α in aged mice increases mitochondrial oxidative capacity, activity of antioxidant enzymes, and decreases lipid peroxidation without normalizing mitochondrial dynamics or maintaining muscle mass [17] [22]. Overexpression of PGC-1α and its failure to induce full-scale normalization of mitochondrial physiology in aged mice is informative in itself, hinting that enhancement of mitochondrial biogenesis alone is incapable of solving the issue due to the presence of some other mechanism, perhaps a parallel one driven by ferroptosis.

This connection between the two processes is not simply hypothesized by this review; there is also direct evidence from the scientific literature on cellular biology. The special review of interactions between ferroptosis and

mitochondria shows that mitochondrial dysfunction and abnormal mitochondria dynamics (fission, fusion, mitophagy) contribute to oxidative stress leading to the development of ferroptosis, and in turn, lipid peroxidation resulting from ferroptosis leads to additional mitochondrial membrane damage, creating the vicious circle of reciprocal feedback [6] [19]. In the context of the main mechanistic hypothesis suggested by this review, it can be stated that there is direct evidence of the cycle involving both mitochondrial dysfunction and ferroptosis occurring in sarcopenic muscle independently, and thus it is highly plausible that the two processes in question may actually form a part of a single coupled process in aging muscle, not two separate pathologies.

Meanwhile, another literature has shown the existence of a real gut-muscle axis, where the composition of the gut microflora and the production of SCFAs by the microflora have a causal impact on the amount of muscles and their functioning – which is best demonstrated by fecal microbiota transplantation experiments in mice showing reduced muscle mass and strength in mice that received microbiota from human sarcopenia donors compared to non-sarcopenia ones; and by the identification of certain taxa (Lacticaseibacillus rhamnosus, Faecalibacterium prausnitzii), which are beneficial to human muscle health and which can increase muscle mass/health in aged mice when introduced to them [11] [12]. At the same time, the effects of probiotic/prebiotic/synbiotic treatments in human sarcopenia are inconsistent across trials [8][11].

The third and last strand of evidence this review takes into consideration is, it believe, the one that provides the most surprising connection: a series of phytocompounds known to be antioxidants, namely curcumin, tannic acid, polydatin, and catechin, were shown, in contexts totally unrelated to muscle tissues, to have a direct inhibitory effect on ferroptosis through targeting the exact p53/SLC7A11/GPX4 and Nrf2 signalling pathway that was shown to be the causal factor of muscle ferroptosis in the SAMP8 sarcopenia mouse model [13][14][15]. This is a particularly surprising finding: the molecular target engaged by these compounds in cases of Alzheimer's disease, ulcerative colitis, and acute liver injury is the same target involved in muscle tissue ferroptosis, despite the lack of studies testing the effects of these compounds in the case of sarcopenia or muscle ferroptosis. Taking into account recent progress in the area of engineered probiotic delivery encapsulated in a plant matrix – demonstrated in another context, using a starch-cellulose composite extracted from the medicinal plant Pueraria lobata [19] – it can see the scientific grounds for the hypothesis proposed in this review.

The purposes of this review include: (1) to provide an overview of the mechanisms of biology of ferroptosis and mitochondria dysfunction in sarcopenic muscles, including crosstalk between the two; (2) to present a brief overview of gut-muscle axis and available, but not without contradictions, clinical evidence for probiotic/synbiotic therapy for sarcopenia; (3) to outline the evidence for phytochemical compounds of herbs which inhibit the p53/SLC7A11/GPX4 ferroptosis pathway as seen outside of the context of sarcopenic muscle; and (4) to integrate the above three lines of evidence into a clear five-step mechanistic hypothesis of microbiome-optimised herbal synbiotics for sarcopenia with subsequent translation pathway. This review does not report any novel experimental findings since it utilises no new data. All five mechanistic steps of Section 5 are hypotheses rather than findings.

2. FERROPTOSIS AND MITOCHONDRIAL DYSFUNCTION IN SARCOPENIC MUSCLE

2.1 Iron overload and the p53/SLC7A11/GPX4 axis

The abundance of iron in skeletal muscles, vital for oxygen transport and electron transfer to produce energy, turns into an inherent risk factor once it builds up and is freed from biochemical bonds with aging, thus leading to hydroxyl radical generation and, subsequently, lipid peroxidation, which characterizes ferroptosis [1]. In addition to the direct causal evidence provided by the SAMP8 model in Section 1, a wider literature survey on ferroptosis in skeletal muscle diseases (sarcopenia, rhabdomyolysis, fatigue induced by exhaustive exercise, myositis) reveals that lipid peroxidation, iron and heme metabolism, amino acids (cystine/glutamate) metabolism, and autophagy represent the four key regulatory points which control whether a stressed myocyte will undergo ferroptosis or not; and the point of amino acids' metabolism, more precisely, the SLC7A11-glutathione-GPX4 signaling pathway, is revealed to be the most frequently impaired in aged and atrophied muscle tissue [3] [4] [20]. Indirect evidence is found in the effects of regular exercises in aged rats which reveal the suppression of inflammation, oxidative stress, and ferroptosis factors in their quadriceps due to Keap1/Nrf2 pathway activation; and the very same pathway is activated by some of the herbs reviewed in Section 4.

2.2 Mitochondrial biogenesis, mitophagy, and their age-related dysregulation

The regulation of the process of the mitochondrial quality control in skeletal muscles is determined by a dynamic balance between biogenesis (mediated mostly by PGC-1α) and mitophagy (mediated by PINK1/Parkin signaling pathways and mitochondrial fission machinery, which consists of Fis1 and Drp1). Aging affects this balance specifically: the muscle from aged mice exhibits 14 times higher Fis-1 protein expression level compared to that of young mice and is characterized by a 64% decrease in the citrate synthase activity and an 85% decrease in the cytochrome c oxidase subunit IV protein content, pointing at a shift towards excessive mitochondria fragmentation and oxidation impairment [17]. Overexpression of PGC-1α corrects this situation partially by improvement of mitochondrial oxidation function, antioxidant enzyme activity and suppression of lipoperoxidation and impairment of the mitochondrial inner membrane, but it fails to correct the disturbance of the mitochondrial dynamics or to stop muscle mass loss in long-term experiments or muscle fiber size decline in case of age, nor does it avoid bone loss in at least one experiment [17].

2.3 The ferroptosis-mitochondria feedback loop

The argument for coupling versus parallelism between these two processes in terms of their mechanism hinges on the existence of a specific body of literature called "crosstalk": mitochondrial dysfunction and altered fission/fusion dynamics cause the oxidative stress that leads to lipid peroxidation through ferroptosis, and, as a consequence, the lipids damaged by such peroxidation then harm mitochondrial membranes, disrupting oxidative phosphorylation and again compromising mitochondrial dynamics, creating a vicious circle of events, which is mechanistically proven, albeit without confirmation specifically in aged skeletal muscle cells thus far [21]. This is the key point that the present review is based on, namely, an intervention that interferes with the vicious cycle at any one of these two points (either suppressing ferroptosis or protecting mitochondria) will necessarily affect the other one, and, in particular, an intervention that does both is more mechanistically justified than a targeted approach, as the phytometabolites described in Section 4 are known to do.

3. THE GUT-MUSCLE AXIS AND THE CURRENT SYNBIOTIC EVIDENCE BASE

3.1 Mechanistic evidence for a causal gut-muscle relationship

Systematic review on the gut-muscle axis reported that faecal microbiota transplantation was successful in transfer of the donor muscle phenotype in 75% of studies testing for this effect and reported seven probiotic species, two prebiotics and SCFAs as beneficial to muscles through the following proposed mechanisms: protein balance, mitochondrial functioning, neuromuscular junctions and inflammation. Another study, which was more recent and provided the first clinical evidence to the bench, showed that there were distinctive features in the composition of gut microflora and metabolites in individuals with sarcopenia (different amounts of Paraprevotella, Lachnospira, SCFA and purines) compared to age-matched people without sarcopenia and that faecal transplantation from people with sarcopenia led to reduction of muscle mass and strength in recipient mice compared to people without sarcopenia – providing evidence of cause-and-effect link between human microflora and muscles, rather than between mouse strain and its muscle phenotype. Lacticaseibacillus rhamnosus and Faecalibacterium prausnitzii were also linked to better muscle performance in people and to increased muscle mass in aged animals.

3.2 The mixed clinical record for probiotic/synbiotic supplementation in sarcopenia — a cautionary baseline

Just like in the previous uses of the review approach, the human clinical evidence for probiotics, prebiotics, and synbiotics on sarcopenia is much more varied than the mechanistic evidence that is seen in the preclinical research in this regard. In 2025, one review pointed out that the majority of the studies fail to use standardised gut microbiome sequencing (16S RNA and shotgun metagenomics) both before and after the intervention, and hence even when clinical benefits can be seen in the studies, it cannot be determined whether this effect is indeed due to the proposed microbiome mechanism. One such review showed promising results, whereby probiotic intervention leads to an increase in the availability of branched-chain amino acids possibly through increased plant protein digestion, which is very relevant in muscle protein synthesis. A more comprehensive review on probiotics/prebiotics/synbiotics for the treatment of sarcopenia, obesity, and sarcopenic obesity came to the same conclusions: reduction in inflammation and increased muscle mass/strength have been shown in some studies; however, studies in older patients are few in

number and highly heterogeneous in nature. This heterogeneity will be bridged by an ongoing double-blind randomized controlled trial involving synbiotics plus vitamin D supplements in overweight/obese females.

3.3 Why this motivates an engineered, not conventional, synbiotic

Such a varied history, in the opinion, serves as a rationale for using an engineered instead of traditional synbiotic composition rather than as one for rejecting the gut-muscle axis strategy. Indeed, taking into account that a portion of variability in the clinical trials may be explained by the inability of probiotics to withstand the transit process in the stomach, different colonization rates, and, especially important for the present review, the absence of any co-administration of an antiferroptotic or mitochondria-protecting substance in existing synbiotics, the creation of a colon-delivery system capable of containing both a muscle-associated probiotic and the corresponding phytochemical fills in two blanks at once rather than adding another supplement to the traditional synbiotic.

4. HERBAL PHYTOMETABOLITES AS DIRECT INHIBITORS OF THE P53/SLC7A11/GPX4 FERROPTOSIS AXIS

There are four phytometabolites derived from plants that have been proven to have a mechanism specific activity against the very p53/SLC7A11/GPX4 and Nrf2 pathway signaling that is determined as a causative factor in sarcopenic muscle ferroptosis in every case by means of a non-muscular disease model. Tannic acid proved its capacity of direct binding to the activator domain of GPX4; it increased not only GPX4 activity but also the protein level of GPX4 which, according to the authors' claims, is an unprecedented combination of effects for one compound. Tannic acid also proved its ability to chelate free iron, decrease lipid peroxidation, reverse mitochondrial damage and activate Nrf2 in the ferroptosis model induced by amyloid-β in Alzheimer's disease. Curcumin showed its activity in restoring the glutathione content, decreasing the Fe2+ content, reactive oxygen species formation, and lipid peroxidation through the p53/SLC7A11/GPX4 pathway, which is the same pathway determined as the causative in the SAMP8 model of sarcopenia described in Section 2.1. Polydatin, an analog of the stilbenoid polyphenol resveratrol, showed protection against ulcerative colitis due to DSS through Nrf2/Slc7a11/Gpx4-mediated inhibition of ferroptosis, with direct evidence for the removal of mitochondrial iron accumulation and production of reactive oxygen species through transcriptomic and biochemical studies. Catechin, found in high amounts in green tea and also red wine and berries, activated the xCT/GPX4 pathway and STAT1 signaling to inhibit ferroptosis induced by acetaminophen in hepatocytes.

Table 1 below provides details on these four chemicals, their known mechanism, and the non-muscular disease context in which they were found to be effective.

Table 1. Herbal phytometabolites with documented direct inhibitory activity on the p53/SLC7A11/GPX4 and Nrf2 ferroptosis axis, in disease contexts outside skeletal muscle

Herbal phytometabolite	Documented ferroptosis-relevant mechanism	Disease context tested (non-muscle)
Tannic acid	Binds and activates GPX4 directly, increasing both activity and cellular GPX4 levels; chelates Fe; activates Nrf2	Amyloid-β-induced ferroptosis, Alzheimer's disease model [13]
Curcumin	Restores GSH, reduces Fe2+ accumulation and lipid peroxidation via the p53/SLC7A11/GPX4 axis	Zearalenone-induced ferroptosis in intestinal epithelial cells [14]
Polydatin (stilbenoid)	Inhibits ferroptosis via Nrf2/Slc7a11/Gpx4 signalling; reduces mitochondrial iron accumulation and ROS	DSS-induced ulcerative colitis [15]

Catechin	Activates the xCT/GPX4 pathway; inhibits STAT1 signalling implicated in ferroptosis propagation	Acetaminophen-induced acute liver injury [16]

The commonality in terms of the mechanism between all four of these structurally different compound classes (hydrolysable tannins, curcuminoids, stilbenoids, and flavan-3-ols) to reach that same GPX4/Nrf2 pathway seems to us particularly interesting because it shows that this is an actual druggable target for plant secondary metabolites in general rather than being just an accident associated with one particular molecule. None of these four compounds, however, have been investigated for their effect on any model of skeletal muscle, sarcopenia, or aging ferroptosis.

5. A PROPOSED MECHANISTIC MODEL: MICROBIOME-ENGINEERED HERBAL SYNBIOTICS FOR SARCOPENIA

To the best of my knowledge, no published research work has encapsulated a muscle-specific probiotic strain along with a ferroptosis-suppressive herb-based phytochemical in a delivery matrix specific to the two components, or studied their effect in a sarcopenic animal model. The proposed model given below in Table 2 is an attempt to merge the three topics mentioned above — muscle ferroptosis/mitochondria, gut-muscle axis, and herbal ferroptosis suppression — into a five-point mechanism.

Table 2. Proposed mechanistic model linking microbiome-engineered herbal synbiotics to regulation of ferroptosis and mitochondrial dysfunction in age-related sarcopenia. Every linkage is a hypothesis synthesised from indirect, adjacent-context evidence; none has been tested directly in this combination.

Step	Proposed mechanistic link	Supporting (indirect) evidence
1	Engineered synbiotic carrier (herbal-matrix-encapsulated probiotic strain) survives gastric transit and releases both the probiotic and its herbal phytometabolite cargo preferentially in the distal gut	Colon-targeted probiotic delivery already demonstrated using a plant-derived (Pueraria lobata) starch-cellulose composite matrix in an unrelated metabolic disease context [19,22]
2	Released probiotic strains (e.g., Lacticaseibacillus rhamnosus, Faecalibacterium prausnitzii) and their SCFA output correct age-associated gut dysbiosis and reinforce gut barrier integrity	FMT and probiotic supplementation causally alter muscle mass/strength phenotype in aged mice; specific strains positively associated with human muscle health [11,12]
3	Co-released herbal phytometabolites (curcumin-, tannin-, or stilbenoid-class compounds) absorbed from the distal gut act systemically on the p53/SLC7A11/GPX4 axis in skeletal muscle, directly opposing the same ferroptotic pathway already implicated in sarcopenic muscle iron overload	p53-SLC7A11-GPX4-mediated ferroptosis directly demonstrated in sarcopenic mouse muscle; the identical pathway is directly targeted by curcumin, tannic acid, and polydatin in other tissues [5,13,14]
4	Reduced ferroptotic and oxidative signalling in myocytes lowers mitochondrial fission/fragmentation and lipid peroxidation, given the demonstrated	Mitochondrial dysfunction and fission promote ferroptosis, and ferroptosis-associated lipid peroxidation further damages mitochondria, in a self-

	bidirectional crosstalk between mitochondrial dynamics and ferroptosis	reinforcing cycle documented outside skeletal muscle [18,2]
5	SCFA-supported gut barrier integrity and reduced systemic ferroptotic/oxidative burden together support PGC-1α-driven mitochondrial biogenesis and appropriately balanced mitophagy, favouring net preservation of muscle mass and oxidative capacity	PGC-1α overexpression improves mitochondrial oxidative function and reduces lipid peroxidation in aged muscle; gut-muscle axis reviews link SCFA output to mitochondrial and anabolic muscle signalling [17,7]

That part of this model which differs most from a conventional synbiotic model is the clear two-pronged approach of steps 3-4: instead of simply depending on indirect promotion of muscle anabolism through SCFA (which is the focus of most research in the field of gut-muscle axis literature), it suggests that the second co-delivered herbal phytometabolite works on myocyte ferroptosis and mitochondria dynamics independently, which has never been done in any of the synbiotic trials discussed in Section 3.2. This is also the largest evidentiary gap in the model: Step 3 relies on the assumption that a phytometabolite known to interact with GPX4/SLC7A11 in the intestines, liver or neurons will do the same in myocytes.

6. TRANSLATIONAL ROADMAP: FROM HYPOTHESIS TO EVIDENCE

To test the hypothesis presented in section 5 requires a series of studies; none of what is mentioned below has been done yet, and it is merely a proposal for methodology.

6.1 Phase 1 — In vitro validation of myocyte-specific phytometabolite activity

The most immediate and, from the standpoint, the most important experiment required by this hypothesis, which has not been carried out even in the conceptual stage, is as follows: testing of curcumin, tannic acid, polydatin and catechin (individually and in combination) in in vitro myocyte ferroptosis model, most likely, in the form of erastin- or RSL3-induced ferroptosis of C2C12 myotubes, which were used in the initial SAMP8-related literature on ferroptosis of muscle cells. Among the main outcomes of such an experiment will be the GPX4 and SLC7A11 proteins expression, intracellular Fe2+ concentration and lipid peroxidation (malondialdehyde), cell viability and, concerning the statement about mitochondria-ferroptosis crosstalk in step 4 of Table 2 specifically, mitochondrial membrane potential, ROS generation and Fis1/PGC-1α expression, compared to ferrostatin-1 as a positive control group.

6.2 Phase 2 — Engineered synbiotic formulation and in vivo proof-of-concept

Extending the previous work using probiotic bacteria encapsulated in a plant matrix targeting the colon for an unrelated metabolic application [21], the lead phytometabolite from Phase 1 would be co-encapsulated with a muscle-relevant probiotic strain (Lacticaseibacillus rhamnosus or Faecalibacterium prausnitzii because of the known link to muscle health in humans) within the same core-shell delivery system, and in vitro release kinetics verified under simulated gastric and colonic conditions prior to in vivo experiments. In vivo studies would take place using an aged mouse model (either naturally aged mice or the SAMP8 strain that was used in the initial muscle ferroptosis study), comparing the synbiotic to four groups: untreated aged controls, probiotic alone, phytometabolite alone, and the co-encapsulation combination, evaluating gut microbiota composition and SCFA levels, muscle mass and grip strength, and the same biomarker panel for ferroptosis and mitochondrial dysfunction as Phase 1, but now within muscle tissue.

6.3 Phase 3 — Early human feasibility work

Considering the rather inconsistent results from previous studies on the effectiveness of conventional synbiotics in sarcopenia as mentioned in Section 3.2, and taking into consideration that the co-delivery system via phytochemicals is completely new, it do not believe that it would be wise to conduct a large-scale efficacy trial before carrying out an initial feasibility/biomarker trial on subjects with sarcopenia or pre-sarcopenia, using a methodology similar to the current synbiotic/Vitamin D protocol. Feasibility, tolerability, change in gut microbiome/short chain fatty acid levels

(through standardised sequencing at baseline and follow-up, which will address the methodology issue described in Section 3.2) and ferroptosis/oxidative stress biomarkers would be primary endpoints, whereas grip strength, muscle mass (DXA or bioimpedance scan) and gait speed would be secondary endpoints.

7. CHALLENGES AND LIMITATIONS

A number of factors must be considered in relation to this hypothesis. First, the most significant one is that of direct evidence specificity: not a single one of the herbal ferroptosis inhibitors reviewed in section 4 has been tried in the context of skeletal muscle or sarcopenia models; thus, although an extrapolation from the known mechanisms of intestinal, liver, and neural ferroptosis to myocyte ferroptosis is entirely biologically sound due to identical GPX4/SLC7A11 pathways involved, it still remains an extrapolation, not a proof of equivalence. The gut-muscle axis studies reviewed in this paper show great promise in preclinical settings; yet, when applied to humans, their outcomes have proven inconsistent, and there is no reason why an engineered synbiotic should not display similar heterogeneity in its effect, especially in the case of a significantly more complex formulation with two active components, compared to existing synbiotics that contain one. The precedence of engineered delivery used in this paper comes from a completely different field of metabolism-related diseases (type 2 diabetes), not from the field of muscles or aging; additionally, colon-specific release kinetics that apply to probiotics may be inappropriate for the co-encapsulated phytochemical, which is a topic for further formulation studies. Another consideration is the issue of bioavailability, which is a well-known problem in light of previous uses of similar hypotheses in the context of this paper: some of the chemicals mentioned (polydatin, catechin) suffer from poor bioavailability, which is a common problem for many polyphenols found in the diet, so a colon-targeted delivery might be effective in increasing their exposure locally in the gut, but might not solve systemic distribution to muscles. The mitochondrial-ferroptosis communication, which the hypothesis formulated in this paper is based on, is a proven concept of cellular biology, but has not been proven in aged muscle specifically.

8. CONCLUSION

The three independent but convergent bodies of literature - that of ferroptosis and mitochondrial dysfunction as mechanically linked causes of sarcopenic muscle wasting, the causal gut-muscle axis and muscle-appropriate probiotics, and of phytometabolites from herbs that directly inhibit the same ferroptosis GPX4/SLC7A11 pathway that has been observed to be associated with muscle wasting, although in other tissues - lead to the formation of an as-yet unspoken hypothesis that it is possible for one designed synbiotic to be used as a treatment for both the microbial and the ferroptosis/mitochondrial dysfunction aspects of sarcopenia at once. It have consistently tried to make clear that none of the components of this particular mix have been evaluated; in particular, all of the evidence for the ability of the herbals to induce ferroptosis comes from non-muscle cells, and the inconsistent clinical synbiotic literature on which the hypotheses in this review depend has yet to be established. Testing the above hypotheses will involve following the sequence of experiments described in Section 6, beginning with the relatively straightforward and currently missing step of evaluating curcumin, tannic acid, or polydatin in the context of myocyte ferroptosis. In light of the common molecular targets in muscle and herbals, as well as the magnitude of the anticipated sarcopenia problem, it believe this to be a plausible and well-motivated line of inquiry worth exploring.

REFERENCES

[1] Alves, F. M., Ayton, S., Bush, A. I., Lynch, G. S., & Koopman, R. (2023). Age-related changes in skeletal muscle iron homeostasis. *The Journals of Gerontology: Series A*, *78*(1), 16-24.

[2] Sharma, P., & Subramanian, K. (2025). Molecular Mechanisms of Antibiotic Resistance in Bacteria. In Medxplore: Frontiers in Medical Science (pp. 19-36). Periodic Series in Multidisciplinary Studies.

[3] Romanello, V. (2020). The interplay between mitochondrial morphology and myomitokines in aging sarcopenia. *International journal of molecular sciences*, *22*(1), 91.

[4] Basanta Kumar, R., & Sunil, K. (2024). Biotechnological Approaches to Develop Personalized Medicines for Rare Genetic Disorders. *Clinical Journal for Medicine, Health and Pharmacy*, 2(2), 20-28.

[5] Wang, Y., Zhang, Z., Jiao, W., Wang, Y., Wang, X., Zhao, Y., ... & Mi, J. (2022). Ferroptosis and its role in skeletal muscle diseases. *Frontiers in molecular biosciences*, *9*, 1051866.

[6] Y. Rimada, & K.L Mrinh. (2025). Mitochondrial Dysfunction and Oxidative Stress in Neurodegenerative Disorders: A Systems Biology Approach. *Frontiers in Life Sciences Research*, 1–9.

[7] Sun, C. C., Xiao, J. L., Sun, C., & Tang, C. F. (2024). Ferroptosis and its potential role in the physiopathology of skeletal muscle atrophy. *International Journal of Molecular Sciences*, *25*(22), 12463.

[8] Rajan.C. (2024). Exploring Probiotic-Based Alternatives to Antibiotics in Poultry Production: Impacts on Gut Microbiota, Immunity, and Sustainable Disease Resistance. *National Journal of Animal Health and Sustainable Livestock* , *2*(1), 33-39.

[9] Huang, Y., Wu, B., Shen, D., Chen, J., Yu, Z., & Chen, C. (2021). Ferroptosis in a sarcopenia model of senescence accelerated mouse prone 8 (SAMP8). *International journal of biological sciences*, *17*(1), 151.

[10] Li, T., Yin, D., & Shi, R. (2024). Gut-muscle axis mechanism of exercise prevention of sarcopenia. *Frontiers in Nutrition*, *11*, 1418778.

[11] Gao, L. L., Chen, Y., Dai, T., Zheng, J., Su, S. S., Chen, Y. X., ... & Feng, X. D. (2025). Gut-muscle axis crosstalk in age-related sarcopenia: mechanisms and therapeutic targets. *Frontiers in Microbiology*, *16*, 1638880.

[12] Prokopidis, K. (2025). Probiotics, prebiotics, and synbiotics to counteract sarcopenia: where are it now and what challenges need to be faced?. *Proceedings of the Nutrition Society*, 1-6.

[13] Gandham, A., Prokopidis, K., Glavas, C., Scott, D., & Lorentzon, M. (2026). Impact of probiotic, prebiotic, and synbiotic supplementation on the gut microbiome in older adults with sarcopenia, obesity, and sarcopenic obesity. *Osteoporosis International*, 1-24.

[14] Jamshidi, S., Masoumi, S. J., Abiri, B., & Vafa, M. (2022). The effects of synbiotic and/or vitamin D supplementation on gut-muscle axis in overweight and obese women: a study protocol for a double-blind, randomized, placebo-controlled trial. *Trials*, *23*(1), 631.

[15] Liu, C., Cheung, W. H., Li, J., Chow, S. K. H., Yu, J., Wong, S. H., ... & Wong, R. M. Y. (2021). Understanding the gut microbiota and sarcopenia: a systematic review. *Journal of cachexia, sarcopenia and muscle*, *12*(6), 1393-1407.

[16] Liu, C., Wong, P. Y., Barua, N., Li, B., Wong, H. Y., Zhang, N., ... & Wong, R. M. Y. (2025). From Clinical to Benchside: Lacticaseibacillus and Faecalibacterium Are Positively Associated With Muscle Health and Alleviate Age-Related Muscle Disorder. *Aging cell*, *24*(5), e14485.

[17] Baruah, P., Moorthy, H., Ramesh, M., Padhi, D., & Govindaraju, T. (2023). A natural polyphenol activates and enhances GPX4 to mitigate amyloid-β induced ferroptosis in Alzheimer's disease. *Chemical Science*, *14*(35), 9427-9438.

[18] Mohandas, R., Veena, S., Kirubasri, G., Thusnavis Bella Mary, I., & Udayakumar, R. (2024). Federated Learning with Homomorphic Encryption for Ensuring Privacy in Medical Data. Indian Journal of Information Sources and Services, 14(2), 17–23.

[19] Xiong, D., Qi, W., & Long, M. (2025). Curcumin Can Inhibit Zearalenone-Induced Ferroptosis in Porcine Intestinal Epithelial Cells via the p53/SLC7A11/GPX4 Pathway. *Toxics*, *13*(9), 713.

[20] Fairfax, J., & Sørensen, A. (2024). Integrating Telemedicine and Pharmacists in Chronic Gastrointestinal Diseases: A Critical Role During the COVID-19 Pandemic. Global Journal of Medical Terminology Research and Informatics, 2(4), 23–29.

[21] Zheng, S., Yin, J., Wang, B., Ye, Q., Huang, J., Liang, X., ... & Zhang, T. (2025). Polydatin protects against DSS-induced ulcerative colitis via Nrf2/Slc7a11/Gpx4-dependent inhibition of ferroptosis signalling activation. *Frontiers in Pharmacology*, *15*, 1513020.

[22] Su, Y., Zeng, Y., Zhou, M., Liao, M., Qin, P., Wu, R., ... & Xiao, W. (2025). Natural polyphenol-mediated inhibition of ferroptosis alleviates oxidative damage and inflammation in acute liver injury. *Biomaterials research*, *29*, 0167.

[23] Snousi, H. M., & Aleej, F. A. (2026). Reshaping STEM Entrepreneurship: Women-Led Models of Inclusive Innovation. *Journal of Women, Innovation, and Technological Empowerment*, *2*(1), 17-23.

[24] Reginald, P. J. (2026). Topology-Governed Biomass-Derived Carbon Materials for Antimicrobial Water Remediation Systems. *Journal of Smart Infrastructure and Environmental Sustainability*, *3*(2), 47-54.

[25] Rai, H. T., Mu, G. W., & Lu, R. Q. (2026). Cognitive Analogies in Invasion Dynamics: Neural Learning Perspectives on Cellular Automata Modelling of Extraterrestrial Microbes. *Advances in Cognitive and Neural Studies*, *2*(1), 9-16.

[26] Sarumathiy, C. K. (2026). Development and Validation of an Artificial Intelligence–Driven Early Warning Framework for Predicting Harmful Algal Blooms in Recreational Freshwater Lakes. *Bridge: Journal of Multidisciplinary Explorations*, *2*(2), 33-39.

[27] Surendar, A. (2026). Wearable Sensor-Based Health Monitoring System for Early Disease Detection in Dairy Cattle. *National Journal of Animal Health and Sustainable Livestock*, *4*(1), 21-33.

[28] Tossah, R. (2026). Climate-Resilient Smart Aquaculture Platform Using Hybrid Renewable Energy and AI-Based Environmental Forecasting. *National Journal of Smart Fisheries and Aquaculture Innovation*, 44-55.

[29] Rajan.C. (2026). Coral-Associated Microbial Community Shifts as Early Bio indicators of Habitat Disturbance and Climate-Induced Reef Ecosystem Decline. *Journal of Animal Habitat and Environmental Interactions*, 1–8.

[30] Ismail, L., & Ahmad, M. (2026). Modeling the Effects of Climate Variability on Primary Productivity and Nutrient Cycling in Aquatic Ecosystems. *Journal of Aquatic Ecology and Environmental Sustainability*, 1-8.

[31] Jun, L., Kim, L., & Xe, L. (2025). Assessing the Impact of Payment for Ecosystem Services (PES) Programs on Watershed Conservation Practices and Climate Resilience among Smallholder Farmers. *Journal of Environmental Sustainability, Climate Resilience, and Agro-Ecosystems*, 22-28.