The American Journal of Applied Sciences
ISSN 2689-0992 Volume 08 - 2026

Proceedings of Women in Academia, Research and Management for Work-life Initiatives for Sustainable Health & Empowering Safety (WARM-WISHES 2026)

In Silico Exploration of Natural Compounds and Drug Repurposing Strategies for FOXO3a Modulation in Metabolic and Autoimmune Muscle Disorders

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Received: 19 Apr 2026 | Received Revised Version: 28 Apr 2026 | Accepted: 13 May 2026 | Published: 22 May 2026

DOI: 10.37547/tajas/warm-11

Abstract

Chronic inflammation, oxidative stress, energy-defective intermediates homeostasis has been gradually recognized in their relevant diseases: metabolic disorders and autoimmune muscle disease including myositis. Forkhead box O3a (FOXO3a), an important transcription factor plays important role in regulating essential cellular processes such as stress response, apoptosis, metabolism homeostasis, and muscle protein turnover. Recent advances in computational biology have allowed for high-throughput screening of FOXO3a-targeting molecules in silico. Flavonoids and polyphenols are different subcategories of phytochemicals that gained attraction due to their remarkable antioxidant, anti-inflammatory, and multi-target abilities. At the same time, drug repurposing strategy is a cost-effective approach because it identifies new therapeutic uses for known approved drugs which have an established safety profile. Here, we review FOXO3a in metabolic and autoimmune muscle disease. It also emphasizes the use of in silico methods to screen phytochemicals and repurposed drugs that may target FOXO pathways as novel therapies for future pharmacologic development.

Keywords: FOXO3a, Therapeutic targets, Myositis, In Silico Drug Discovery, Drug repurposing, Phytochemicals.

Cite This Article: Das, T., Singh, P., Tufail, E., & Sanyal, S. (2026). In Silico Exploration of Natural Compounds and Drug Repurposing Strategies for FOXO3a Modulation in Metabolic and Autoimmune Muscle Disorders. The American Journal of Applied Sciences, 101–106. https://doi.org/10.37547/tajas/warm-11

1. Introduction

Metabolic disorders including Diabetes Mellitus, Obesity, and Metabolic Syndrome are marked by abnormalities in carbohydrate and fat metabolism, persistent mild inflammation, and elevated oxidative stress. These factors typically cause problems with skeletal muscle function, cardiovascular malfunction, and metabolic balance issues. Similar to that, muscle inflammatory and autoimmune diseases like Polymyositis, Dermatomyositis, and Inclusion Body Myositis result from chronic inflammation of muscle cells resulting in weakening and poor physical performance (Yang et al., 2019).

Both metabolic and inflammatory myopathies develop due to a number of cellular mechanisms responsible for processes such as oxidative damage, inflammation, apoptosis, regulation of proteolysis, and protein synthesis. The molecules involved in these processes include FOXO3a, which is currently attracting attention within science due to its vital role in metabolic functions and stress responses (Accili et al., 2004, Eijkelenboom et al., 2013).

FOXO3a belongs to the family of Forkhead box O transcription factors. Its activation can be regulated through several signalling pathways, including PI3K/Akt pathway, AMPK signalling, and Insulin signalling (Calnan et al., 2008). Under physiological conditions, FOXO3a facilitates oxidation protection, recycling through autophagy, and maintaining metabolic balance. Overactivation of FOXO3a, however, could result in muscle atrophy, apoptosis, and metabolic abnormalities. Because of these functions, the FOXO3a factor is considered an important pharmaceutical target.

Traditional methods of drug discovery are generally long, expensive, and demanding on resources. As a result, various computational techniques, including molecular docking, virtual screening, and ADMET profiling, have been employed in recent times in order to find promising compounds that regulate FOXO3a activity in a timely and cost-effective manner. The present review considers the involvement of FOXO3a in metabolic and autoimmune muscle disorders. It also emphasizes the usage of in silico techniques for assessing phytochemicals and repurposed drugs as possible treatment for FOXO pathways in drug discovery.

2. FOXO3a and Its Involvement in Metabolic and Autoimmune Muscle Disorders

The FOXO3a gene codes for a protein transcriptional factor which regulates the expression of genes that are involved in stress response against oxidative stress, control of cell cycle, programmed cell death, autophagy, and energy homeostasis (Greer et al., 2005; Calnan et al., 2008; Fasano et al., 2019). FOXO3a activation may be elicited in response to different stimuli, among which are nutrient shortage, oxidative stress, or inhibition of the Akt Signaling Pathway (Brunet et al., 1999). This way, FOXO3a helps cells cope with stress conditions (Greer et al., 2005; Calnan et al., 2008; Fasano et al., 2019,).

In metabolic diseases particularly in diabetes disruption of Insulin signalling can result in sustained activation of FOXO3a (Accili *et al*., 2004, Cheng *et al*., 2010). Abnormal FOXO3a activation leads to poor glucose tolerance, high level of reactive oxygen species and metabolic disturbances. Moreover, FOXO3a is a factor that controls hepatic glucose production and lipid metabolism thus creating direct connection to complications that arise from metabolic disorders.

In case of skeletal muscle, it is worth noting that FOXO3a is related to protein degradation. Increased expression of FOXO3a increases expression of proteins that are involved in breakdown of skeletal muscle through ubiquitin-proteasome pathways (Eijkelenboom *et al*., 2013). Proteins such as Atrogin-1 and MuRF1 are regulated by FOXO3a. Therefore, an increase in activity of FOXO3a is directly associated with muscle wasting disorders such as Cachexia and various inflammatory muscle disorders. In muscle autoimmune diseases like dermatomyositis and polymyositis, pro-inflammatory cytokines like tumor necrosis factor-alpha and interleukin-6 interfere with the intracellular pathway controlling the regulation of FOXO3a resulting in oxidative stress and autophagic dysfunction and muscle wasting (Brunet et al., 1999, Li *et al*., 2016). Figure 1 gives an schematic representation on the role of FOXO3a in muscular disorder.

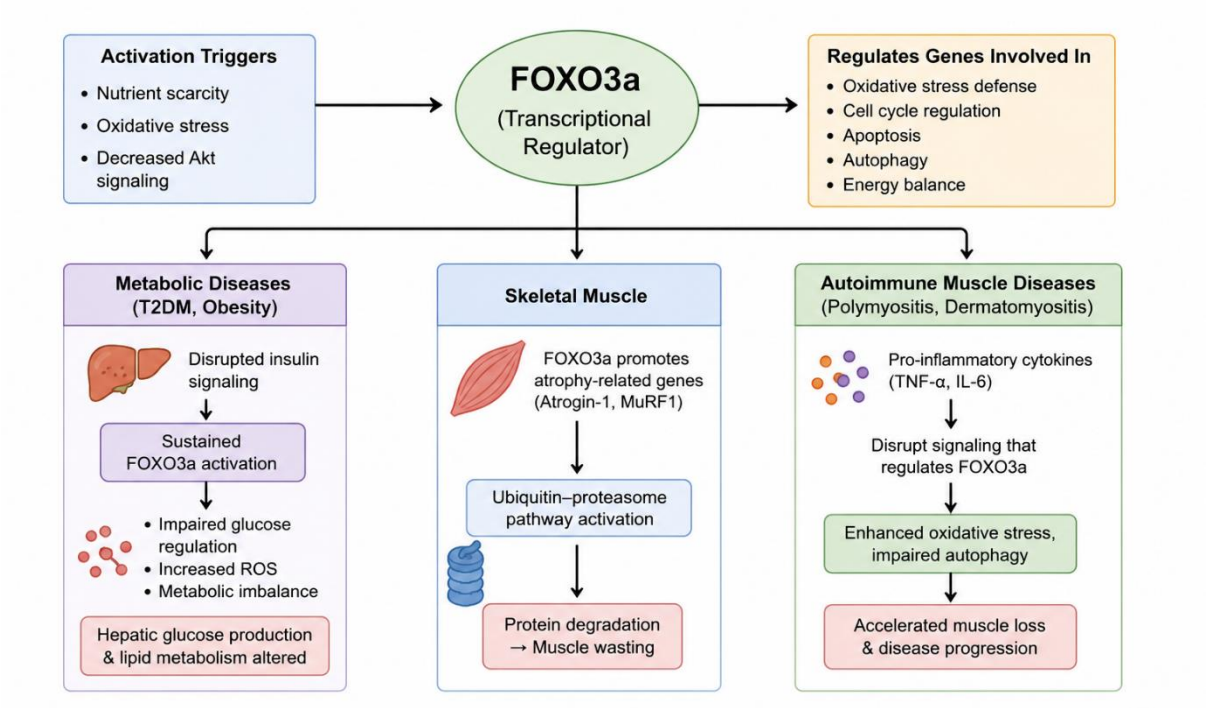

Figure 1. *Role of FOXO3a in metabolic dysfunction and autoimmune muscle disorders.*

3. Phytochemicals as Potential FOXO3a Modulators

Phytochemicals refer to biologically active molecules found naturally in plants, seeds, fruits, vegetables, and medicinal herbs. Such chemicals are scientifically popular since they contain numerous biological activities including antioxidants, anti-inflammation, anti-diabetic and cytoprotective propertie (Kumar *et al*., 2013, Panche *et al*., 2016). Due to these properties, phytochemicals serve as potential agents for the prevention and management of chronic metabolic and inflammatory diseases.

Phytochemicals have been divided into various classes; out of all, flavonoids stand out as the best researched class (Panche et al., 2016). The common examples include Quercetin, Luteolin, Kaempferol, Genistein, and Myricetin. These compounds are responsible for regulating a variety of cell processes related to oxidative damage, inflammation, and metabolic dysfunction. Their polyphenolic chemical composition allows interaction with multiple molecular targets like enzymes, signaling, and transcriptional proteins.

Several pathways could be employed by flavonoids to regulate FOXO3a protein. For instance, these compounds are able to modulate the PI3K/Akt Pathway that determines the regulation and intracellular localization of FOXO3a. Additionally, some phytochemicals could activate the AMPK signaling pathway that plays a crucial role in regulating cellular energy homeostasis. Moreover, flavonoids reduce oxidative stress by suppressing the production of ROS molecules. Flavonoids also inhibit the production of inflammatory mediators like TNF-α and IL-6, as well as genes linked to apoptosis and cell survival processes (Habrowska et al., 2021).

Since the phytochemicals influence several pathways simultaneously, they have a capability of being multitargeted. The feature is highly beneficial in cases where conditions such as metabolic disorder, inflammation, oxidative stress, and tissue damage coexist. In this respect, their broad influence might provide an advantage compared to drugs targeted for just one molecular target. Another important benefit of phytochemicals is their generally favourable safety profile. Their natural origin, lower toxicity in many cases, and presence in common dietary sources increase their suitability as potential long-term therapeutic agents for managing metabolic disorders and autoimmune muscle diseases (Babalola *et al*., 2025).

4. Drug Repurposing Strategies for FOXO3a Modulation

Drug repurposing, which is the finding of new therapeutic uses for existing or previously tested drugs, has also developed as a strategy to facilitate the process of drug discovery with lower cost and risks (Pushpakom et al., 2019). The rationale for its importance is that its pre-existing safety, pharmacokinetic and toxicity profiles will mitigate development uncertainty, thus accelerating the delivery to clinic. In the context of FOXO3a-targeted therapy, computational approaches can be used to screen existing drugs for potential modulatory effects on this transcription factor. In silico approaches that are commonly used includes are molecular docking and ADMET prediction, to treat drug–target interactions and rationalize candidates with high binding affinities with pharmacological properties. Drugs like Palonosetron, Tadalafil, Darifenacin can be repurposed for targeting FOXO3a. While such drugs are not classical direct FOXO3a modulators, their already established roles in specific signaling pathways like cyclic GMP signaling and receptor-mediated responses or cellular stress regulation suggest potential indirect effects on FOXO3a-associated mechanisms such as oxidative stress, apoptosis, inflammation and metabolic homeostasis (Rojas et al., 2010, Andersson, 2018). Thus, this kind of interactions between networks seems to be involved in complex conditions like the metabolic syndrome and inflammatory myopathies. In addition, such an approach offers a reasonable foundation for further experimental support as well as provides the basis for novel treatments targeting FOXO3a deregulation in chronic muscular diseases.

5. In Silico Approaches in drug repurposing and phytochemical screening

In-silico approaches have become an essential component of recent drug discovery and phytochemistry (Meng et al., 2011). These techniques help screen large compound libraries faster and at a cheaper cost in comparison with conventional experimental assays. In studies on FOXO3a, in silico methodologies can be especially helpful in selecting suitable molecules for subsequent validation experiments.

5.1. Molecular Docking

Molecular docking can be described as a computer-aided simulation of the binding process between the ligand and the protein receptor active or functional site (Morris et al., 2009; Trott et al., 2010). This computational methodology predicts the preferred orientation of the ligand within the receptor active site as well as its binding energy (Morris et al., 2009). In FOXO3a, molecular docking has become an integral step in screening phytochemicals and approved drugs.

5.2. Virtual Screening

Virtual Screening is utilized to analyze huge compound libraries either natural or synthesized. This technique is aimed at identifying molecules exhibiting structure similarities, favorable physicochemical characteristics or strong affinity towards the target protein (Giordano *et al*., 2022). It considerably decreases the number of molecules to be analysed later on.

5.3. ADMET Prediction

ADMET Prediction helps calculate such important parameters as absorption, distribution, metabolism, excretion and toxicity of particular compounds (Daina et al., 2017). These calculations allow identifying drug-like molecules and discarding those with low bioavailability or adverse effects (Lipinski et al., 2001).

5.4. Molecular Dynamics

Molecular Dynamics Simulations provide comprehensive data concerning the movement and stability of particular protein-ligand complex. Based on this approach one can determine how stable the interaction between the protein and chosen ligand is at physiological conditions. All described computational approaches allow developing the effective cost-efficient methodology for identification of potential FOXO3a modulators.

6. Conclusion

FOXO3a is an important player in oxidative stress, apoptosis, metabolism, and regulation of protein turnover in skeletal muscle cells. Dysfunction in FOXO3a is highly linked to metabolic syndromes and autoimmune muscle conditions such as Myositis. Recent research indicates that natural phytochemical compounds, especially flavonoid molecules such as Quercetin and Kaempferol, can efficiently modulate the FOXO3a-associated pathways by virtue of their antioxidant and anti-inflammatory effects. Furthermore, repositioned drugs such as Palonosetron, Tadalafil, and Darifenacin are considered as potential targets for FOXO3a by modulating the stress response and metabolic pathways. Molecular docking, ADMET

prediction, and structural validation can be regarded as reliable computational methods for discovering potential therapeutic agents for the above conditions. In conclusion, a combination of phytochemical compounds and repositioned drugs could serve as a useful platform to explore therapeutic interventions for diseases related to FOXO3a.

Author's contribution: TD: Data curation, Literature study, Writing original draft, Illustrations. PS: Data curation, Analysis, Writing original draft, Illustrations. ET: Supervision, Reviewing & editing the original draft SS: Conceptualization, Supervision, Reviewing & editing the original draft.

Author Declaration Statements

Declaration: The authors hereby declare that the manuscript submitted for consideration is an original work and has not been published or submitted elsewhere for publication. The authors take full responsibility for the integrity, accuracy, and ethical compliance of the work presented in the manuscript.

Conflict of Interest: All authors confirm that:

Any potential conflicts of interest, whether financial or non-financial, have been fully disclosed. – **Yes / Not Applicable**√

All sources of funding and financial support received for the conduct of the study have been appropriately acknowledged. **– Yes / Not Applicable**√

Necessary ethical approvals have been obtained from the relevant institutional or regulatory bodies for studies involving human participants, animals, or sensitive data, wherever applicable. **– Yes / Not Applicable**√

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