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PPAR γ as a Therapeutic Target in Myositis: Current Perspectives on Repurposed Drugs and Phytochemicals

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Abstract

Myositis refers to a cluster of rare chronic autoimmune disorders defined by muscle inflammation and progressive weakness. Standard therapy such as corticosteroids and immunosuppressants has considerable toxicity associated with them and is frequently ineffective in controlling the disease. Peroxisome proliferator-activated receptor gamma (PPAR γ), a ligand activated nuclear receptor, has been implicated in myositis as well for its function on the regulation of inflammation and metabolism. PPAR γ activation inhibits inflammatory pathways including, in particular, NF- κ B signaling and guides immune resolution. In this review, the mechanistic role of PPAR γ in myositis is discussed and drug repurposing, a strategy to screen for well-known FDA-approved compounds with putative PPAR γ -modulating activity, is considered. Moreover, the similarities between phytochemicals (in particular flavonoids) and small molecules render the former as natural ligands

Keywords: Myositis, PPAR γ , Drug repurposing, Phytochemicals.

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1. Introduction

Myositis is a rare autoimmune disorder characterized by chronic inflammation and progressive muscle weakness, significantly impairing daily activities and quality of life. It includes major subtypes such as polymyositis, dermatomyositis, and inclusion body myositis, each differing in presentation but sharing immune-mediated muscle damage. Currently, therapies employ corticosteroids and immunosuppressants that have many adverse side effects and do not offer consistent long-term relief. Peroxisome proliferator-activated receptor gamma (PPAR γ), a nuclear receptor implicated in metabolic and inflammatory regulations, has been identified as an effective target in autoimmune diseases. PPAR γ activation inhibits essential pro-inflammatory mechanisms such as the NF- κ B pathway and encourages anti-inflammatory immune responses, ensuring tissue safety from immune system attacks (Straus & Glass, 2007; Manickam et al., 2020). Thiazolidinediones are well-established agonists of PPAR γ with anti-inflammatory activity; nonetheless, their application is restricted due to safety issues. Drug repurposing, which involves identifying new uses for existing drugs, presents a viable strategy in the search for novel treatments (Ashburn & Thor, 2004; Pushpakom et al., 2019, Mishra et al. 2024). In the same way, phytochemicals, specifically flavonoids, have been proposed as alternative PPAR γ modulators. They possess diverse structures, multiple targets, reduced toxicity levels, and have extensive human exposure history, offering excellent therapeutic potentials (Liu et al., 2020, Chen & Wang, 2025). In this review article, a comprehensive analysis of the role played by PPAR γ in myositis is provided, with an emphasis on the potential repurposing of phytochemicals and FDA-approved drugs.

2 Types of Myositis

Myositis is a rare autoimmune disease characterized by the misrecognition by the immune system of self-versus nonself, resulting in the attack of muscle tissues causing inflammation and weakness of the affected areas (Mammen, 2010; Raquel et al., 2025). This disease occurs quite rarely, with only one to ten individuals per 100,000 suffering from the disease worldwide (Dalakas,

2015). For the affected, carrying out activities such as brushing the hair and climbing stairs becomes rather hard. The major types of Myositis include polymyositis, dermatomyositis, and inclusion body myositis. Polymyositis typically involves symmetric involvement of muscle tissue (Dalakas, 2015). On the other hand, dermatomyositis has the additional presence of a skin rash. Finally, the third type of myositis, inclusion body myositis is characterized by the weakening of thigh muscles and forearm muscles in old age patients, resulting in frequent falls and poor grip strength. Unlike the other two diseases where women tend to be affected much more, inclusion body myositis tends to occur more commonly among men. Polymyositis and dermatomyositis are mostly common among females (Needham & Mastaglia, 2007). Another disease associated with myositis is known as inclusion body myositis. The disease is described as an illness that affects the muscles gradually, causing inflammation and wasting. It was noted that this form of the disease is normally detected when one reaches his or her forty fifth birthday, and progresses in a steady manner each year. Persons suffering from this form of disease will realize that their symptoms begin as weakness in thigh muscles and hands, making it difficult for them to undertake activities such as walking upstairs or getting out of chairs, and even handling objects becomes difficult. As the disease continues its progression, swallowing also becomes increasingly difficult. What goes on inside the person's body during the development of the disease is that the body attacks the muscle fibers with abnormal protein substances (Renato & Paolo 2013). Concerning the treatment of the condition, it is essential to mention that there is no way how the problem could be reversed at the moment. Thus, the primary task is in the management of the disease through physiotherapy and taking into consideration the need for safety measures to avoid fall-related accidents and providing assistance when dealing with swallowing issues.

Besides muscle weakness, patients often report pain in their joints, fatigue and difficulty swallowing, and, sometimes, even inflammation of the lungs (Dalakas, 2015). When taken together, all these symptoms make the daily routine complicated. Moreover, the lack of adequate management results in additional

complications. In the course of development, the condition is associated with various risks to people's health because no treatment options are available. In this case, physicians apply management strategies that are focused on reducing the inflammation by means of steroids. However, a long use of steroids is harmful since a person becomes overweight, suffers from bone weakening, diabetes, and infections (Oddis & Aggarwal, 2018). Sometimes, the issue requires the prescription of other drugs, such as methotrexate, azathioprine, and mycophenolate mofetil (Aggarwal & Oddis, 2011).

Because treatment choices are available are very few in number there are many patients that still struggle with active disease symptoms and the side effects that come with the medicines. There is a real need for treatments that are safer and more targeted towards myositis so that inflammation can be controlled without causing too much damage to the body even after a prolonged use. And therefore one such approach is to repurpose those drugs that are already approved by the FDA for other conditions and see if they can be given a new purpose for treating myositis. Some of these drugs work through a protein called PPAR γ which has been proved to play an important role in calming down inflammation in autoimmune conditions (Liu *et al.*, 2020).

3. Role of PPAR γ in myositis

PPAR γ also called Peroxisome proliferator-activated receptor Gamma belongs to a family of proteins called nuclear receptors. In inflammation, PPAR γ acts as a brake. It shuts down NF κ B, a major inflammatory switch inside cells and the production of inflammatory signals like tumor necrosis factor alpha and interleukin 6 drops significantly. These molecules are the reasons behind the redness, swelling and tissue damage seen in autoimmune conditions. Activating PPAR γ also pushes immune cells toward a calming role. Macrophages switch from an aggressive state to a healing state, dendritic cells become less effective at activating other immune cells and T cells are guided away from attacking healthy tissues (Straus & Glass, 2007). Muscle tissue carries PPAR γ receptors, which is significant in case of myositis. When inflammation increases significantly in the muscles, PPAR γ steps in and helps reduce damage. PPAR γ activation protects muscle cells from inflammatory signals and helps maintain normal muscle function, making it a natural target for conditions where muscle inflammation is the main problem (Figure 1) (Manickam *et al.*, 2020).

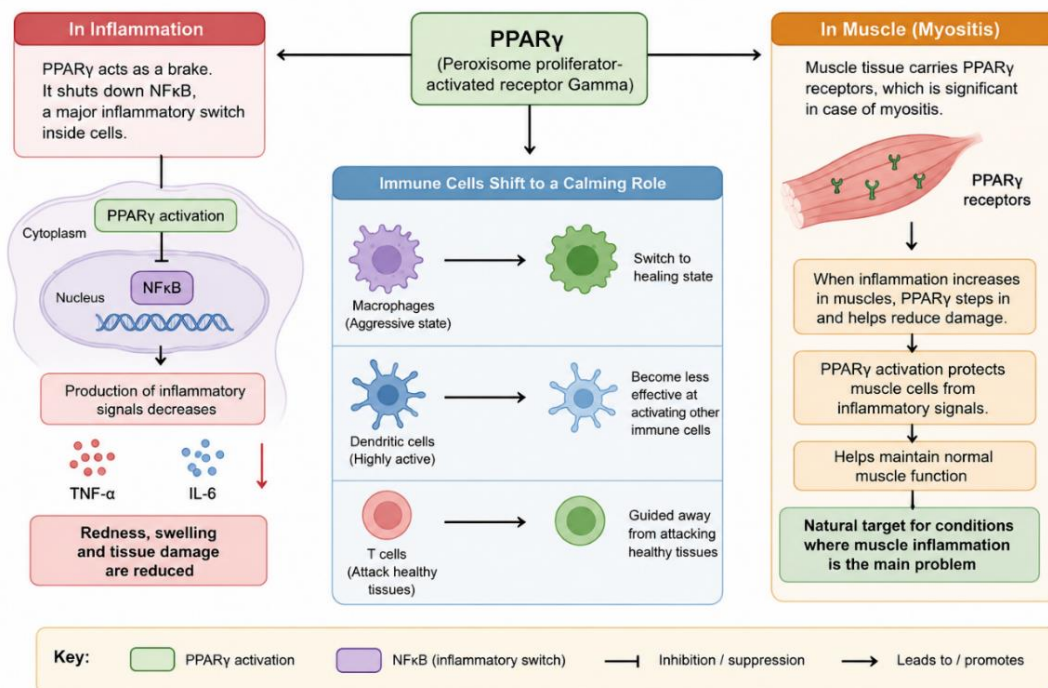


Figure 1. Anti-inflammatory and protective role of PPAR γ in myositis.

4. PPAR γ as a Therapeutic Target

PPAR γ is a nuclear receptor and transcription factor, commanding certain genes to turn themselves on or off. Due to this mechanism, it is considered a powerful regulator for many biological processes including inflammation. These processes include processes ranging from how sugars and fats are used by the body to how inflammation is controlled. There are three members in this family, PPAR α , PPAR γ , and PPAR $\beta\delta$ and each of these has its own unique role. PPAR γ is best known for its work in managing blood sugar levels and fat storage, which is why drugs like pioglitazone and rosiglitazone were originally developed for diabetes treatment.

Since PPAR γ has this built in ability to calm inflammation and protect tissues, it makes a lot of sense to explore it as a target for treating myositis because myositis is also an autoimmune condition. If drugs already exist that can safely turn on PPAR γ , they may serve a new purpose in managing this disease. Thiazolidinediones like pioglitazone and rosiglitazone are well known PPAR γ activators that have been used for years in diabetes patients to deal with insulin spike (Soccio *et al.*, 2014). But other drugs made for different purposes may also act as an activator of PPAR γ and bring it into action.

5. Drug Repurposing Strategy for PPAR γ to combat inflammation

Drug repurposing refers to the identification of new therapeutic indications for existing drug and FDA-approved compounds, which significantly reduces time- and cost-associated barriers compared with de novo drug development. These drugs have already been through extensive clinical trials, giving a good understanding of their safety profile, pharmacokinetics and adverse effects allowing for skipping early-stage trials; thereby helping to expedite the translational pipeline (Ashburn & Thor, 2004, Pushpakom *et al.*, 2019;). Novel therapeutic approaches are especially beneficial in rare diseases like myositis, as limited treatment options and low patient populations makes standard drug development difficult (Nosengo 2016).

In this context, PPAR γ was considered a prime candidate due to its potent anti-inflammatory property. Thiazolidinediones (TZD), like pioglitazone, rosiglitazone and troglitazone, also belong to the category of repurposing agents that are highly selective

PPAR γ activators used to treat type 2 diabetes by increasing insulin sensitivity (Soccio *et al.*, 2014). In addition to their metabolic properties, these drugs have also proven to be very effective in anti-inflammatory action and may serve as candidates for treatment of autoimmune diseases like myositis (Evans *et al.*, 2004). However, their application is restricted owing to safety issues (Nissen & Wolski, 2007); some of the TZDs have also been discontinued whereas others have been associated with side effects; hence, the need for development of an alternate agent targeting PPAR γ .

6. Phytochemicals as Modulators of PPAR γ

Phytochemicals refer to the group of naturally occurring chemical substances extracted from plants, and these have been attracting considerable attention as potential modulators of PPAR γ owing to their ability in anti-inflammation and their relative safety (Chen & Wang, 2025). One of the phytochemicals studied extensively for its anti-inflammatory activity includes flavonoids (Leyva-López *et al.*, 2016). Furthermore, they have several targets and can prove to be more effective in a disease whose pathology is described as “multi-faceted” like myositis. The varied structures of these compounds increase the possibility of increased flexibility in the binding of the PPAR γ active site. In silico analysis can be helpful in screening out compounds that not only prove to be efficacious but also are safe pharmacologically (Daina *et al.*, 2017).

7. Conclusion

The current study suggests PPAR γ as a potential target for developing therapies for myositis since it regulates inflammatory signaling pathways while protecting muscle tissues from immune-mediated damage. Through a drug repurposing strategy, the research shows how FDA-approved drugs could potentially be redirected for use against myositis, thus providing a quicker and less expensive way of developing new treatments than conventional drug discovery. Furthermore, by studying phytochemicals, especially flavonoids, this research increases the possibility of identifying suitable candidates for myositis therapy owing to their natural origin, diverse chemical structures, and anti-inflammatory properties. In addition, molecular docking helps to understand how the selected compounds interact with the PPAR γ receptor at a molecular level, allowing one to identify compounds that bind strongly and are biologically relevant.

Author's contribution: AC: Data curation, Literature study, Writing original draft, Illustrations. AP: 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**✓
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- 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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