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# THE THEORETICAL MODULATION OF THE NLRP3 INFLAMMASOME BY 17B-ESTRADIOL BASED GAHT IN CELLULAR AGING: A SCOPING REVIEW

# A MODULAÇÃO TEÓRICA DO INFLAMASSOMA NLRP3 PELA THAG BASEADA EM 17B-ESTRADIOL NO ENVELHECIMENTO CELULAR: UMA REVISÃO DE ESCOPO

# LA MODULACIÓN TEÓRICA DEL INFLAMASOMA NLRP3 POR LA THAG BASADA EN 17B-ESTRADIOL EN EL ENVEJECIMIENTO CELULAR: UNA REVISIÓN EXPLORATORIA

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## ABSTRACT

This study aims to map and synthesize the available scientific literature on the impact of affirmative hormone therapy on the molecular regulation of the NLRP3 inflammasome and the progression of neuroimmunological inflammaging in aging transfeminine individuals. In this scenario, 17β-estradiol emerges as a master regulator of immunometabolic homeostasis. However, a profound translational gap exists in geroscience regarding the transfeminine population, unlike cisgender women experiencing menopause, trans women maintain continuous, exogenous estradiol levels through Gender-Affirming Hormone Therapy (GAHT) during the aging process. To map this dynamic, a scoping review was conducted guided by the JBI Institute guidelines and the PRISMA-ScR checklist, analyzing the biomedical literature published from 2013 onwards. The literature establishes that estrogen deprivation acts as the primary trigger for the assembly of the NLRP3 complex and microglial hyperreactivity. In contrast, the prolonged maintenance of estrogenic signaling promoted by GAHT acts as a true immunometabolic and epigenetic shield. By keeping hormone receptors actively engaged in silencing cellular alarm pathways (such as the NF-κB cascade), GAHT chronically represses NLRP3 activation, preventing the degradation of neuroplasticity and peripheral oxidative stress. This continuous modulation also serves as a crucial buffer against allostatic load and minority stress, preserving immunological resilience via epigenetic axes (e.g., miR-138-5p/SIRT1/HMGB1). 17β-estradiol-based GAHT transcends phenotypic congruence, establishing itself as a highly complex systemic physiological intervention. The uninterrupted suppression of NLRP3 radically alters the biological course of immunosenescence, providing trans women with the neurobiological and vascular foundation necessary for resilient and cognitively preserved aging.

**Keywords:** Gender-affirming Hormone Therapy. 17β-estradiol. NLRP3 Inflammasome.

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**RESUMO**
Este estudo visa mapear e sintetizar a literatura científica disponível sobre o impacto da terapia hormonal de afirmação de gênero na regulação molecular do inflamassoma NLRP3 e na progressão do inflammaging (inflamação associada ao envelhecimento) neuroimunológico em indivíduos transfemininos em processo de envelhecimento. Nesse cenário, o 17β-estradiol emerge como um regulador central da homeostase imunometabólica. No entanto, existe uma profunda lacuna translacional na gerociência em relação à população transfeminina: diferentemente das mulheres cisgênero na menopausa, as mulheres trans mantêm níveis contínuos e exógenos de estradiol por meio da Terapia Hormonal de Afirmação de Gênero (THAG) durante o envelhecimento. Para mapear essa dinâmica, realizou-se uma revisão de escopo orientada pelas diretrizes do Instituto JBI e pela lista de verificação PRISMA-ScR, analisando a literatura biomédica publicada a partir de 2013. A literatura estabelece que a privação de estrogênio atua como o principal gatilho para a montagem do complexo NLRP3 e para a hiper-reatividade microglial. Em contrapartida, a manutenção prolongada da sinalização estrogênica promovida pela THAG atua como um verdadeiro escudo imunometabólico e epigenético. Ao manter os receptores hormonais ativamente engajados no silenciamento de vias de alarme celular (como a cascata NF-κB), a THAG reprime cronicamente a ativação do NLRP3, prevenindo a deterioração da neuroplasticidade e o estresse oxidativo periférico. Essa modulação contínua também serve como um amortecedor crucial contra a carga alostática e o estresse de minoria, preservando a resiliência imunológica por meio de eixos epigenéticos (ex.: miR-138-5p/SIRT1/HMGB1). A THAG baseada em 17β-estradiol transcende a congruência fenotípica, estabelecendo-se como uma intervenção fisiológica sistêmica de alta complexidade. A supressão ininterrupta do NLRP3 altera radicalmente o curso biológico da imunossenescência, proporcionando às mulheres trans a base neurobiológica e vascular necessária para um envelhecimento resiliente e com preservação cognitiva.

**Palavras-chave:** Terapia Hormonal de Afirmação de Gênero. 17β-estradiol. Inflamassoma NLRP3.

**RESUMEN**
Este estudio tiene como objetivo mapear y sintetizar la literatura científica disponible sobre el impacto de la terapia hormonal de afirmación de género en la regulación molecular del inflamasoma NLRP3 y la progresión del envejecimiento inflamatorio neuroinmunológico (inflamación asociada al envejecimiento) en personas transfemeninas mayores. En este contexto, el 17β-estradiol emerge como un regulador central de la homeostasis inmunometabólica. Sin embargo, existe una profunda brecha traslacional en gerociencia con respecto a la población transfemenina: a diferencia de las mujeres cisgénero en la menopausia, las mujeres trans mantienen niveles continuos y exógenos de estradiol a través de la terapia hormonal de afirmación de género (THAG) durante el envejecimiento. Para mapear esta dinámica, se realizó una revisión exploratoria, guiada por las directrices del Instituto JBI y la lista de verificación PRISMA-ScR, analizando la literatura biomédica publicada desde 2013. La literatura establece que la privación de estrógeno actúa como el principal desencadenante del ensamblaje del complejo NLRP3 y de la hiperreactividad microglial. En contraste, el mantenimiento prolongado de la señalización de estrógeno promovido por THAG actúa como un verdadero escudo inmunometabólico y epigenético. Al mantener los receptores hormonales activamente involucrados en la supresión de las vías de alarma celulares (como la cascada NF-κB), THAG reprime crónicamente la activación de NLRP3, previniendo el deterioro de la neuroplasticidad y el estrés oxidativo periférico. Esta

modulación continua también sirve como un amortiguador crucial contra la carga alostática y el estrés de las minorías, preservando la resiliencia inmunológica a través de ejes epigenéticos (p. ej., miR-138-5p/SIRT1/HMGB1). THAG basado en 17β-estradiol trasciende la congruencia fenotípica, estableciéndose como una intervención fisiológica sistémica altamente compleja. La supresión ininterrumpida de NLRP3 altera radicalmente el curso biológico de la inmunosenescencia, proporcionando a las mujeres transgénero la base neurobiológica y vascular necesaria para un envejecimiento resiliente con preservación cognitiva.

**Palabras clave:** Terapia Hormonal de Afirmación de Género. 17β-estradiol. Inflamasoma NLRP3.

## 1 INTRODUCTION

The transfeminine and gender diverse population constitutes a significant portion of global society that has achieved greater longevity alongside the advancement of gender affirming care policies (Coleman *et al.*, 2022; Winter *et al.*, 2016). At the epicenter of this care lies Gender Affirming Hormone Therapy (GAHT). For transgender women and travestis, this lifelong intervention relies on androgen suppression and the continuous, exogenous administration of estrogens, notably 17β-estradiol (Hembree *et al.*, 2017; T'Sjoen *et al.*, 2019). As this population reaches chronological senescence, the intersection of chronic GAHT use and systemic aging alterations poses new challenges for biomedical research. This dynamic reveals a critical gap in current geriatric guidelines (Iwamoto *et al.*, 2023).

At the core of the biology of senescence is inflammaging, a chronic, systemic, low-grade inflammatory state driven by the hyperactivation of the NLRP3 inflammasome (Ferrucci & Fabbri, 2018; Franceschi *et al.*, 2018; Swanson *et al.*, 2019). This multiprotein complex acts as a cellular damage sensor. In the central nervous system, it is the primary mediator of neuroinflammation and cognitive decline through microglial hyperreactivity (Heneka *et al.*, 2018; Thakkar *et al.*, 2018). Pathophysiological literature robustly establishes that resilience to this process inherently depends on sex hormones. 17β-estradiol acts as a potent transcriptional inhibitor of NLRP3. However, this knowledge is largely based on estrogen deprivation models, such as ovarian failure in cisgender menopause or animal castration models (Dong *et al.*, 2023; Klein & Flanagan, 2016).

Applying this biological model to the transfeminine population is inadequate, and it neglects the endocrinological reality of GAHT. Trans women maintain stable, exogenous estradiol levels over decades, while operating under severe allostatic load generated by chronic minority stress (White Hughto *et al.*, 2015; Winter *et al.*, 2016). This neuroendocrine storm acts as a constant trigger for inflammaging. It is imperative to investigate whether the continuous maintenance of exogenous estrogen concentrations in later life acts as a persistent molecular shield, capable of halting NLRP3 hyperactivation, or whether the wear imposed by social vulnerabilities negatively recalibrates this homeostasis (Kodi *et al.*, 2024; Wan *et al.*, 2026; White *et al.*, 2022).

Given the scattered evidence regarding the intersection of GAHT and immunosenescence, this study aims to map and synthesize the available scientific literature on the impact of affirmative hormone therapy on the molecular regulation of the NLRP3 inflammasome and the progression of neuroimmunological inflammaging in aging

transfeminine individuals. By elucidating these mechanisms, this research seeks to provide evidence to optimize affirmative care guidelines in senescence, and to promote health equity (Coleman *et al.*, 2022; De Silva *et al.*, 2024).

## 2 METHODOLOGY

This study is a scoping review, rigorously conducted in accordance with the Joanna Briggs Institute guidelines (Peters *et al.*, 2020) and reported using the PRISMA-ScR (Tricco *et al.*, 2018). The methodological protocol was publicly registered on the Open Science Framework platform under the DOI identifier 10.17605/OSF.IO/URJZS. The research question relied on the PCC mnemonic (Population, Concept, and Context) to investigate the extent of evidence concerning the influence of Gender Affirming Hormone Therapy on NLRP3 inflammasome modulation and inflammaging within the central nervous system of transfeminine individuals. As this study is a scoping review of previously published literature, Institutional Review Board (IRB) approval and informed consent were not required.

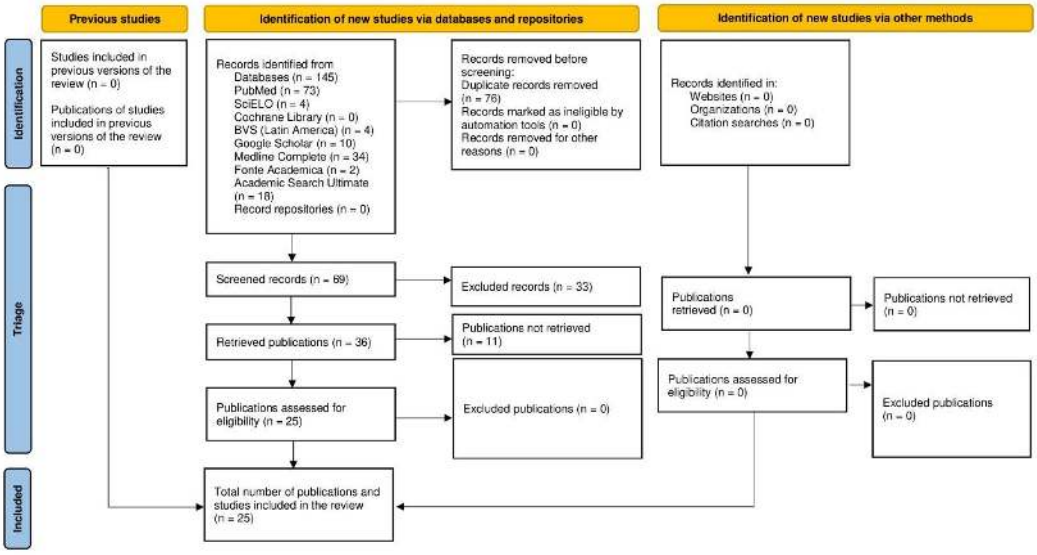
## 3 RESULTS AND DISCUSSION

### 3.1 STUDY SELECTION AND CHARACTERISTICS

The initial electronic search identified 145 records. After duplicate removal, the screening of titles and abstracts filtered 69 articles. Full text reading resulted in a final sample of 25 eligible publications. The complete methodological screening process is detailed in the PRISMA-ScR flowchart (Figure 1), and the synthesis of pharmacological characteristics composes Table 1. The mapping reveals a protagonism of Northern Hemisphere research and an alarming scarcity of data from Latin America (Bai *et al.*, 2020; De Rivero Vaccari *et al.*, 2016; Heitzer *et al.*, 2016; Kangas *et al.*, 2014; Lammerding *et al.*, 2015). Methodologically, there is a predominance of in vivo preclinical trials based on young rodents subjected to ovariectomy to simulate menopause, revealing an age paradox in aging modeling (Bai *et al.*, 2020; Lammerding *et al.*, 2015).

**Figure 1**

*Flowchart of the study identification and selection process for the scoping review, adapted from the PRISMA 2020 model (PAGE et al., 2021)*




Source: Prepared by the authors, 2026.

**Table 1**

*Summary of the methodological characteristics and main results of the included studies*

| Reference (Author, year) | Country | Study Design and Model | Key Outcomes |
|---|---|---|---|
| BAI et al. (2020) | China and USA | In vivo (female Sprague-Dawley rats, global cerebral ischemia model) and in vitro (primary hippocampal neuron culture). | Estrogenic activation via the GPER receptor attenuated neuroinflammation by significantly reducing the expression of NLRP3 and ASC proteins, as well as inhibiting caspase-1 activation and IL-1β maturation in hippocampal microglia. |
| BYNUM; EDWARDS (2026) | USA | Literature Review. | Estrogen signaling acts as a biological protectant that limits mtROS accumulation. Estrogen deprivation (such as in menopause) leads to mitochondrial damage and mtDNA/cardiolipin leakage, events that hyperactivate the NLRP3 inflammasome and promote neuroinflammation and systemic decline. |
| DE RIVERO VACCARI et al. (2016) | USA | In vivo (Reproductively senescent rats, global cerebral ischemia model). | Periodic treatment with a specific estrogen receptor beta (ER-β) agonist attenuated the innate immune response in the central nervous system. The intervention suppressed inflammasome activation (reducing caspase-1, ASC, and IL-1β) and protected hippocampal neurons against ischemic cell death. |
| FARRUGGIO et al. (2020) | Italy | In vitro (primary human hepatocytes and Huh7.5 cell line simulating cellular fatty acid accumulation/steatosis). | 17β-estradiol and genistein actively protected the cells by preserving mitochondrial membrane barrier potential and curbing cellular oxidative stress. Pharmacological inhibition of the NLRP3 |

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| | | | inflammasome (via MCC950) was found to enhance the protective effects mediated by estrogens. |
| GARCIA-GÓMEZ et al. (2020) | Mexico | Literature review (focusing on the endometriosis microenvironment). | Unlike normal tissues, in endometriotic tissues, hyper-stimulation of the ER-β receptor directly cooperates with the NLRP3 inflammasome and the enzyme caspase-1 to increase the aggressive production of IL-1β. This mechanism modulates apoptotic pathways and induces enhanced cell survival in the face of chronic inflammation. |
| GUO et al. (2025) | China | Literature review (focus on spinal cord injury). | Estrogen actively inhibits NLRP3 inflammasome activity and pro-inflammatory cytokines (such as IL-1β and TNF-α), and modulates microglia polarization via ERα, ERβ, and GPER receptors, thereby attenuating neuroinflammation and reducing neuronal apoptosis. |
| HEITZER et al. (2016) | Germany and Iran | In vivo (Male SOD1(G93A) transgenic mice, a model of Amyotrophic Lateral Sclerosis -ALS). | Treatment with 17β-estradiol significantly reduced the expression of NLRP3 inflammasome proteins, levels of activated caspase-1, and mature IL-1β in the spinal cord, which directly correlated with increased motor neuron survival and improved motor function. |
| ISOLA et al. (2023) | USA | Literature review (focusing on aging and chronic disease). | ERα receptor agonism in microglia (including through the action of analogs such as 17α-estradiol) limits the transition of these cells to pro-inflammatory phenotypes and inhibits pathways associated with cytokines such as IL-1β, protecting the central nervous system against age-related neuroinflammation. |
| KANGAS et al. (2014) | Finland and Italy | Observational / Ex vivo study (postmenopausal monozygotic twins discordant for Hormone Replacement Therapy – HRT). | The use of estrogen-based HRT attenuated serum levels of "inflammaging" markers, reducing molecules such as FasL, miR-21, and miR-146a (the latter being involved in controlling IL-1β production). The data suggest that systemic estrogen deficiency accelerates the chronic inflammatory process. |
| LAMMERDING et al. (2015) | Germany | In vivo (male Wistar rats, transient focal cerebral ischemia model). | Administration of 17β-estradiol after the ischemic insult drastically reduced levels of the proteins NLRP3 (found primarily in neurons) and ASC (found in microglia), suppressing IL-1β maturation and caspase-1 activation in the ischemic penumbra of the cerebral cortex. |
| LU et al. (2025) | China | Literature Review. | 17β-estradiol inhibits NLRP3 inflammasome activation and IL-1β release via PP2A and GPER1 signaling, in addition to bolstering antioxidant defense through receptors such as ER-β. 17α-estradiol exerts sex-specific anti-inflammatory effects, reducing microglial activation in the hippocampus and hypothalamus only in males. |

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| LYU et al. (2026) | China | In vivo (female 3xTg-AD and wild-type mice, Alzheimer's disease model) and in vitro (BV-2 cells, SH-SY5Y cells, microglia, and primary neurons). | ERβ and GPR40 receptors are downregulated in the brains of female patients with Alzheimer's disease and in 3xTg-AD mice. Vincamine (acting as a GPR40 receptor agonist) suppressed neuroinflammation via the GPR40/NF-κB/NLRP3 pathway, reducing levels of NLRP3, IL-1β, and cleaved caspase-1 proteins. |
| MAJIDPOOR et al. (2020) | Iran | In vivo (Male Wistar rats; contusion spinal cord injury model at segments T1, T6, and T12). | Spinal cord injury induced increased activity of the NLRP3 inflammasome, ASC, caspase-1, IL-1β, and IL-18 across all evaluated thoracic segments. Treatment with melatonin or E2 reduced NLRP3 protein and IL-1β levels; however, the response was shown to vary by segment (e.g., NLRP3 protein at T6 did not respond to melatonin). |
| MANCINO et al. (2022) | Argentina and Spain | In vivo (female C57BL/6 mice, experimental autoimmune encephalomyelitis [EAE] model). | Administration of tibolone (a compound with tissue-specific estrogenic activity) inhibited the activation of the NLRP3 inflammasome, caspase-1, and IL-1β in the spinal cord. Treatment also significantly reduced astrocytic and microglial reactivity, attenuating the overexpression of TLR4 and HMGB1 and the Akt/NF-κB pathway. |
| MCCARTHY; RAVAL (2020) | USA | Literature Review. | The menopausal transition is a systemic inflammatory phase that increases the brain's vulnerability to injury and neurodegeneration. The loss of endogenous estrogen protection destabilizes mitochondrial functions, hyperactivating the inflammasome mediated by reactive oxygen species (ROS). |
| NAN et al. (2022) | China | In vivo (female C57BL/6 mice, ovariectomy-associated diabetes model – DACI). | Treatment with 17β-estradiol (as well as Forsythoside B) significantly reversed cognitive decline in ovariectomized diabetic females by suppressing hippocampal neuroinflammation (reduction of IL-1β, IL-6, and TNF-α) and modulating synaptic plasticity. |
| REZAIE et al. (2020) | Iran | In vivo (male Wistar rats, T6 spinal cord contusion injury model). | Spinal cord injury increased the expression of NLRP1, NLRP3, and AIM2 inflammasome complexes. Treatment with melatonin or 17β-estradiol reversed these alterations (including reductions in ASC, caspase-1, IL-1β, and IL-18), inducing the suppression of pathways associated with inflammasome synthesis (TLR4/NF-κB) and activation (NOX2/TXNIP). |
| SLOWIK; BEYER (2015) | Germany | Literature Review. | Sex steroids exert potent neuroprotective and anti-inflammatory effects in acute and chronic diseases, attenuating cytokine activity by directly modulating inflammasome activation and their upstream miRNA regulatory network in innate immune cells. |

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| SLOWIK et al. (2017) | Germany | Literature Review. | It highlights that estrogens selectively suppress the activation of the neuroinflammatory cascade in the brain by acting on microglia and astroglia to control the inflammasome platform (inhibiting cytokines such as IL-1β and IL-18), thereby protecting neurons and even attenuating postmenopausal depressive symptoms. |
| SLOWIK et al. (2018) | Germany and Iran | In vitro (primary astrocyte culture and mouse BV-2 microglial cell line under hypoxic conditions). | Hypoxia induced increased expression of IL-1β, NLRP3, and ASC in glial cells. Administration of 17β-estradiol selectively attenuated the expression of IL-1β, ASC, and NLRP3 (primarily in BV-2 cells), thereby acting upstream of caspase-1 activation. |
| THAKKAR et al. (2018) | USA and China | In vivo (young ovariectomized rats, global cerebral ischemia model) and in vitro (BV2 microglial and HT-22 neuronal cell lines). | 17β-estradiol suppressed microglial activation and actively promoted polarization from the M1 (pro-inflammatory) phenotype to the M2 (anti-inflammatory) phenotype in the hippocampus following global cerebral ischemia. The hormonal intervention reduced the production of inflammasome-related cytokines and attenuated neurotoxicity induced by activated microglia. |
| VRACHNIS et al. (2021) | Greece and United Kingdom | Literature Review. | Postmenopausal hormone replacement therapy partially reverses immune senescence and limits the systemic pro-inflammatory state resulting from the cessation of ovarian function. A reduction in the secretion of cytokines mediated by inflammasomes and other cascades (such as IL-1β, IL-6, IL-8, and TNF-α) is observed following the initiation of treatment. |
| XU et al. (2016) | China | In vivo (female C57BL/6 mice, ovariectomy model simulating estrogen deficiency). | Estrogen deficiency activated the NLRP3 inflammasome (increasing IL-1β and IL-18 levels in the hippocampus), leading to depressive and anxiety-like states. Administration of 17β-estradiol and specific ER-β agonists reversed this neuroinflammation and the associated behavioral deficit. |
| ZHANG et al. (2024) | China | In vivo (aged male mice, model of postoperative cognitive dysfunction – POCD). | Treatment with 17β-estradiol improved postoperative cognitive function and protected neurons by attenuating apoptosis, microglial activation, and IL-1β expression. The neuroprotective mechanism was shown to be directly linked to the alleviation of neuroinflammation via modulation of the miR-138-5p/SIRT1/HMGB1 axis. |

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| ZONIS et al. (2018) | USA | In vivo (C57BL/6 mice) and in vitro (human and murine hippocampal neural progenitor cells). | The chemokine Gro1, induced by inflammatory stimuli, promotes neuroblast senescence, suppressing the development of new hippocampal neurons. Administration of 17β-estradiol selectively blunted this inflammation-induced Gro1 expression in the hippocampus, indicating hormone-mediated, tissue-specific protection. |

Source: Prepared by the authors, 2026.

## 3.2 NLRP3 INFLAMMASOME MODULATION IN THE CENTRAL NERVOUS SYSTEM

The literature unanimously demonstrates that estrogenic signaling acts as a molecular brake on the neuroinflammatory cascade. 17β-estradiol deprivation elevates cellular damage sensors and hyperactivates the NLRP3 inflammasome (Xu *et al.*, 2016). Exogenous hormone administration reverses this condition by silencing neuroinflammation in a tissue specific manner. In brain tissue, estrogen induces microglia to abandon the M1 proinflammatory phenotype and adopt the M2 repair profile (Thakkar *et al.*, 2018). This physiological process prevents ASC protein accumulation in glial cells and blocks NLRP3 assembly in neurons, drastically reducing the secretion of neurotoxic cytokines, like IL-1β and IL-18 (Slowik *et al.*, 2018).

## 3.3 THE MITOCHONDRIAL AXIS AND VASCULAR INTEGRITY

Estrogen decline triggers a severe cellular immunometabolic paradox (Bynum & Edwards, 2026). Without the hormonal shield, mitochondria fail, accumulating reactive oxygen species and releasing DNA fragments into the cytoplasm. These cellular components act as internal alarms that uncontrollably trigger the NLRP3 complex (McCarthy & Raval, 2020). This systemic oxidative stress weakens the physical protective barriers of the body, including the intestinal mucosa and the vascular endothelium (Bynum & Edwards, 2026). Continuous 17β-estradiol treatment rescues cellular respiration and restores blood brain barrier integrity, protecting cognition and the cardiovascular system (Farruggio *et al.*, 2020).

## 3.4 THE EPIGENETIC SHIELD AGAINST ALLOSTATIC LOAD

Evidence analysis reveals that 17β-estradiol modulates gene expression to protect the organism against allostatic load and chronic stress (Kangas *et al.*, 2014). The hormone acts epigenetically by suppressing deleterious microRNAs and rescuing crucial protective enzymes, like Sirtuin 1 (Kangas *et al.*, 2014; Zhang *et al.*, 2024). By preventing SIRT1 enzyme degradation, estrogenic signaling halts the release of the HMGB1 alarm protein and

disarms inflammasome assembly before irreversible neuronal damage occurs (Zhang *et al.*, 2024).

### 3.5 THE TRANSFEMININE TRANSLATIONAL GAP

Despite the biological robustness of the neuroimmunological findings, the mapping exposes a profound scientific gap, involving the absolute invisibility of the population undergoing Gender Affirming Hormone Therapy. The entire current theoretical framework focuses exclusively on ovarian failure in cisgender women (Vrachnis *et al.*, 2021). Transgender women and travestis maintain continuous, exogenous 17β-estradiol levels throughout aging and operate under a severe allostatic load driven by minority stress. Biomedical evidence strongly suggests that the uninterrupted maintenance of this affirmative therapy acts as a systemic epigenetic shield, capable of halting inflammaging and protecting the transfeminine brain (Isola *et al.*, 2023).

### 3.6 DISCUSSION

The consolidation of evidence regarding estrogenic modulation of the innate immune system demands a fundamental shift in how science interprets aging and neuroinflammation. Literature unquestionably demonstrates that 17β-estradiol acts as the primary regulator of the NLRP3 inflammasome. While cisgender women experience a loss of this immunological brake during menopause, transfeminine individuals adhering to Gender Affirming Hormone Therapy maintain continuous and stable exogenous 17β-estradiol levels (Isola *et al.*, 2023; Kangas *et al.*, 2014; Vrachnis *et al.*, 2021). This continuous hormonal presence acts as a systemic immunometabolic shield. By blocking the microglial transition to a destructive inflammatory phenotype and maintaining the stability of the blood brain barrier, 17β-estradiol represses pyroptotic cascades and delays natural immunosenescence (Zhang *et al.*, 2024).

This continuous NLRP3 modulation extends its protective effects beyond the central nervous system to vital metabolic axes. Mitochondria act as signaling hubs that dictate the pace of cellular aging, and their function is rigorously orchestrated by estrogen. The maintenance of exogenous 17β-estradiol levels by affirmative therapy serves as a continuous driving force for mitochondrial biogenesis and resilience (Bynum & Edwards, 2026). This endocrine support helps maintain the integrity of tight junctions in the vascular endothelium and gastrointestinal tract, preventing the leakage of bacterial toxins and silencing the hyperactivation of danger receptors. Consequently, continuous estrogenic therapy has the

potential to ward off cardiometabolic diseases that typically accompany inflammaging (Farruggio *et al.*, 2020).

Beyond structural preservation, the impact of this immunological silencing extends deeply into mental health and resilience against allostatic load. The absence of estrogen triggers NLRP3 hyperactivation in the hippocampus, inducing severe depressive and anxious behaviors (Xu *et al.*, 2016). For transgender women, the chronic psychosocial load of minority stress acts as a devastating biological trigger that accelerates cellular aging through deep epigenetic dysregulations. Chronic wear provokes the overexpression of deleterious microRNAs that suppress crucial protective enzymes, like Sirtuin 1 (Zhang *et al.*, 2024). However, the presence of continuous 17β-estradiol has the remarkable capacity to reverse this condition by rescuing the protective SIRT1 pathway and disarming the inflammasome at its source, acting as a perennial molecular buffer against systemic prejudice (Kangas *et al.*, 2014; Zhang *et al.*, 2024).

Recognizing affirmative therapy as a systemic intervention with profound neuroprotective efficacy requires clinical scrutiny. The continuous use of exogenous hormonal formulations carries specific complexities, heavily dependent on the administration route. Transdermal or parenteral routes bypass gastrointestinal and hepatic overload, mimicking physiological hormone release more accurately and safely, without adding thrombotic risks (Vrachnis *et al.*, 2021). Additionally, this scoping review acknowledges methodological limitations, such as the heterogeneity of the included studies, which prevented quantitative meta analyses. This characteristic reflects the current state of the field, where the primary goal resides in qualitative mapping rather than statistical efficacy synthesis.

The true bottleneck for consolidating these therapies lies in the rigid methodological structure of current biomedical science. Transporting findings from cisgender menopause models directly to transgender women is an extrapolation that translational biology can no longer uncritically accept (Isola *et al.*, 2023; Kangas *et al.*, 2014). This manuscript postulates that affirmative therapy acts as a perennial mechanism for reversing inflammaging and suppressing the NLRP3 complex, while raising an urgent scientific manifesto. It is imperative that frontier biomedical research develops in vivo models and longitudinal clinical cohorts, designed specifically to investigate and respect transfeminine physiology. Only through new methodological paradigms will science validate that Gender Affirming Hormone Therapy

transcends phenotypic congruence, establishing itself as a powerful physiological intervention, capable of ensuring a protected and dignified longevity for trans women.

## 4 CONCLUSION

The mapping conducted in this scoping review allows an irrefutable conclusion regarding the biology of aging. 17β-estradiol acts as a master regulator of immunometabolic homeostasis. The drop in its circulating levels functions as the primary trigger for NLRP3 inflammasome hyperactivation and inflammaging consolidation. By transposing this knowledge to the reality of the transfeminine population, this research demonstrates that the endocrine dynamic is completely different. Transgender women and travestis undergoing Gender Affirming Hormone Therapy operate under a continuous and exogenous maintenance of the hormone. This uninterrupted presence means that estrogen receptors remain actively engaged in silencing cellular alarm pathways and inhibiting the NLRP3 complex over the decades.

The implications of this biological process transcend the maintenance of secondary sexual characteristics. At the cellular level, gender affirming therapy acts as a true immunometabolic shield. It induces the microglial repair profile and protects vital organs against bioenergetic failure. Furthermore, the modulation of epigenetic pathways functions as a crucial buffer against the immense physiological wear generated by minority stress. For the potential of this neuroprotection to be achieved in clinical practice, it is urgent to prioritize safe administration routes, such as transdermal, and to overcome reductionist experimental models. Modern medicine must recognize affirmative hormone therapy as a systemic intervention, capable of altering the course of immunosenescence and ensuring a dignified and protected aging for trans women.

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