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Estrogen as a Neuroprotective Agent: Mechanisms and Clinical Implications for Neuroinflammatory Disorders

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Abstract

Neuroinflammatory disorders, including Alzheimer's disease (AD), Multiple Sclerosis (MS), and Parkinson's disease (PD), are characterized by chronic glial activation and the subsequent release of neurotoxic cytokines. Emerging evidence identifies Estrogen (17 β-estradiol) as a multifaceted neuroprotective agent capable of modulating the central nervous system's (CNS) immune response. This review synthesizes current understanding of the molecular mechanisms through which estrogen exerts its effects, primarily via Estrogen Receptors alpha (ERα), beta (ER β), and the G protein-coupled estrogen receptor (GPER). We evaluate estrogen's role in inhibiting microglial polarization

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toward the pro-inflammatory M1 phenotype, promoting mitochondrial bioenergetics, and enhancing synaptic plasticity. Furthermore, the review discusses the "timing hypothesis," which suggests that the efficacy of estrogen therapy is contingent upon the window of administration relative to menopause or disease onset. We also explore the clinical implications of Selective Estrogen Receptor Modulators (SERMs) and the challenges of translating neuroprotective effects into clinical practice without systemic side effects. By bridging the gap between molecular signaling and clinical trials, this paper outlines future directions for estrogen-based therapies as potential disease-modifying interventions for neuroinflammatory and neurodegenerative conditions.

INTRODUCTION

The sexual dimorphism observed in the prevalence and progression of neurodegenerative and neuroinflammatory disorders has long suggested a biological role for sex hormones. Women typically experience a sharper decline in cognitive function post-menopause, while conditions like Multiple Sclerosis (MS) exhibit a higher incidence in females but often follow a more aggressive course in males. At the center of this dichotomy is Estrogen, specifically 17 beta-estradiol (E2), a steroid hormone with profound non-reproductive functions in the brain.

Recent breakthroughs in neurobiology have shifted the perception of estrogen from a peripheral hormone to a potent neuroprotective agent. In the Central Nervous System (CNS), estrogen is not only sequestered from the blood but also synthesized *de novo* within neurons and astrocytes from cholesterol. This "neuroestrogen" acts as a master regulator of brain health, specifically focusing on its ability to quench the "fire" of neuroinflammation.

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1.1 Mechanisms of Neuroprotection

Estrogen exerts its effects through two primary receptor types: the classical nuclear receptors (ER alpha and ER beta) and the membrane-bound G protein-coupled estrogen receptor (GPER1).

1.1.1 Modulation of Microglial Activation

Microglia are the resident immune cells of the brain. In a diseased state, they shift to a pro-inflammatory phenotype, releasing cytokines like TNF-alpha and IL-1 beta. Estrogen suppresses this transition. By binding to ER alpha, E2 inhibits the NF-kappa B signaling pathway—the "master switch" for inflammation—thereby reducing the production of neurotoxic factors (Villa et al., 2016).

1.1.2 Astrocytic Support and Glutamate Homeostasis

Astrocytes provide metabolic support and regulate the chemical environment of neurons. Estrogen enhances the expression of glutamate transporters (like GLT-1), preventing excitotoxicity—a common driver of cell death in Alzheimer's and stroke. Furthermore, E2 stimulates astrocytes to produce neurotrophic factors like Brain-Derived Neurotrophic Factor (BDNF), which aids in neuronal repair (Acaz-Fonseca et al., 2016).

1.1.3 Mitochondrial Integrity and Oxidative Stress

Neuroinflammation is inextricably linked to oxidative stress. Estrogen preserves mitochondrial membrane potential and reduces the generation of Reactive Oxygen Species (ROS). By upregulating antioxidant enzymes like superoxide dismutase (SOD), E2 prevents the "oxidative burst" that often precedes neuronal apoptosis (Engler-Chiurazzi et al., 2017).

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1.2 Clinical Implications: The "Timing Hypothesis"

A critical discovery in recent years is the "Timing Hypothesis." This suggests that the neuroprotective benefits of estrogen are highly dependent on the age and hormonal status of the individual. In the early post-menopausal period, estrogen therapy (ET) appears to reduce the risk of Alzheimer's Disease (AD). However, if initiated years later when the brain has already undergone significant inflammatory changes and ER expression has declined, ET may be ineffective or even detrimental (Zarate et al., 2017).

Table 1. Comparative Role of Estrogen in Neurological Disorders

Alzheimer's (AD)	Higher in Females	E2 reduces A beta plaque accumulation and Tau phosphorylation.
Multiple Sclerosis	Higher in Females	E2 promotes remyelination and suppresses Th1/Th17 immune responses.
Parkinson's (PD)	Higher in Males	E2 protects dopaminergic neurons in the substantia nigra.
Ischemic Stroke	Higher Post-Menopause	E2 limits the size of the infarct by reducing blood-brain barrier (BBB) permeability.

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Estrogen is far more than a "female hormone"; it is a vital architect of the neural landscape. Its ability to modulate the innate immune system of the brain positions it as a primary candidate for therapeutic intervention. However, the future of estrogen-based therapies lies in "precision endocrinology"—developing Selective Estrogen Receptor Modulators (SERMs) that provide neuroprotection without the peripheral risks associated with systemic hormone replacement.

2. Molcular Mechanisms of Estrogen Action

Estrogen is no longer viewed merely as a transcription factor but as a multifaceted signaling scaffold. Its neuroprotective efficacy is derived from a sophisticated "bimodal" signaling approach: slow, stable genomic changes and rapid, dynamic non-genomic membrane signaling. These pathways converge to modulate the cellular environment of the Central Nervous System (CNS).

2.1 Genomic vs. Non-Genomic Signaling: The Dual-Track Defense

The biological effects of 17 beta-estradiol (E2) are mediated by three primary receptors: the classical nuclear receptors (ER-alpha and ER-beta) and the more recently characterized G protein-coupled estrogen receptor (GPER1/GPR30).

The Classical Genomic Pathway (Nuclear Signaling)

In the genomic model, E2 diffuses through the lipophilic plasma membrane and binds to ER-alpha or ER-beta in the cytoplasm. This binding induces a conformational change, causing the receptors to dimerize and translocate into the nucleus. Once inside, the ER-dimer binds directly to specific DNA sequences known as **Estrogen Response Elements (EREs)** located in the promoter regions of target genes.

This process, while taking hours to manifest, provides long-term structural resilience to neurons. Key upregulated targets include:

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- **Anti-apoptotic proteins:** Specifically **Bcl-2** and **Bcl-xL**, which prevent mitochondrial pore formation and subsequent cytochrome c release.
- **Antioxidant Enzymes:** Enhancement of **Superoxide Dismutase (SOD)** and **Glutathione Peroxidase** expression, which fortifies the cell against oxidative stress (Zarate et al., 2017).
- **Neurotrophins:** Increased transcription of **BDNF** (Brain-Derived Neurotrophic Factor), essential for synaptic plasticity.

The Non-Genomic Pathway (Membrane Signaling)

In contrast, the non-genomic pathway occurs within seconds. This is largely mediated by **GPER**, located in the plasma membrane and endoplasmic reticulum, as well as membrane-associated fractions of classical ERs.

Upon E2 binding, GPER triggers the activation of secondary messenger cascades:

1. **PI3K/Akt Pathway:** This is the primary "survival" circuit. Akt phosphorylates and inactivates **Bad** (a pro-apoptotic protein) and inhibits **GSK-3 beta**, a kinase heavily implicated in the formation of Tau tangles in Alzheimer's Disease.
2. **MAPK/ERK Pathway:** This cascade is vital for maintaining **synaptic density** and dendritic spine morphology. Rapid ERK activation promotes the phosphorylation of **CREB** (cAMP Response Element-Binding protein), bridging the gap between rapid membrane signaling and long-term gene expression (Engler-Chiurazzi et al., 2017).

2.2 Modulation of Glial Cells: Quenching the Inflammatory Fire

Neuroinflammation is not a static state but a dynamic process driven by the "over-activation" of microglia and astrocytes. Estrogen acts as a "glial switch," favoring homeostatic and reparative phenotypes over neurotoxic ones.

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2.2.1 Microglial Polarization: From M1 to M2

Microglia are the primary immune effectors of the CNS. When they sense damage-associated molecular patterns (DAMPs), they adopt a **pro-inflammatory (M1)** phenotype. Estrogen intervenes in this process through several distinct mechanisms:

- **Inhibition of NF-kappa B:** E2 prevents the translocation of the NF-kappa B p65 subunit into the nucleus. This effectively shuts down the production of "cytokine storms" involving **TNF-alpha**, **IL-1 beta**, and **IL-6** (Villa et al., 2016).
- **M2 Polarization:** Recent studies show that E2 promotes the **M2 (anti-inflammatory/reparative)** phenotype. This state is characterized by the release of **IL-10** and **TGF-beta**, which facilitate the clearance of cellular debris (phagocytosis) without causing collateral tissue damage (Tansey et al., 2022).
- **NLRP3 Inflammasome Suppression:** Estrogen has been shown to inhibit the assembly of the NLRP3 inflammasome, a multi-protein complex responsible for the maturation of IL-1 beta, which is a major driver of neurodegeneration in Parkinson's and Stroke.

2.2.2 Astrocyte Support: Maintaining the Synaptic Microenvironment

Astrocytes are the most abundant cells in the brain, responsible for maintaining the Blood-Brain Barrier (BBB) and regulating neurotransmitter levels. Under chronic stress, astrocytes become "reactive," contributing to scar formation (gliosis).

Estrogen preserves astrocytic function via:

- **Glutamate Clearance:** One of the most lethal aspects of neuroinflammation is **excitotoxicity**. Estrogen upregulates the expression of **GLT-1 (EAAT2)** transporters in astrocytes. This ensures that excess glutamate—the brain's primary excitatory

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neurotransmitter—is rapidly cleared from the synaptic cleft, preventing neuronal "over-firing" and subsequent death (Panicker et al., 2021).

- **Metabolic Coupling:** E2 enhances the astrocyte-neuron lactate shuttle, ensuring that even during inflammatory stress, neurons have a steady supply of energy substrates.
- **Chemokine Regulation:** Estrogen limits the production of **CCL2**, a chemokine that recruits peripheral immune cells (like T-cells and macrophages) into the brain, thereby preventing the escalation of a localized inflammatory response into a systemic one.

Table 2. Summary of Estrogen Receptor (ER) Subtypes, Cellular Distribution, and Specific Neuroprotective Mechanisms in the Central Nervous System.

ER-alpha	Nucleus / Cytoplasm	NF-kappa B inhibition; Bcl-2 upregulation	Anti-inflammation; Anti-apoptosis
ER-beta	Nucleus / Mitochondria	Mitochondrial bioenergetics; Antioxidant	Reduced oxidative stress; ATP stability
GPER	Plasma Membrane	PI3K/Akt and MAPK/ERK activation	Rapid survival signaling; Synaptic plasticity

The table No. 2 delineates the distinct functional roles of the three primary estrogen receptors—ER-alpha, ER-beta, and GPER—in mediating brain health. It highlights a multi-layered defense system: ER-alpha focuses on long-term genomic stability and anti-apoptotic signaling, while ER-beta is critical for maintaining mitochondrial efficiency and

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reducing oxidative stress. Complementing these, the membrane-bound GPER facilitates rapid, non-genomic survival signaling through kinase cascades. Together, these receptors illustrate how estrogen acts as a "master regulator," balancing immune response, metabolic energy, and synaptic integrity to provide comprehensive neuroprotection.

3. Estrogen and Specific Neuroinflammatory Disorders

The decline of systemic estrogen—whether through natural menopause, surgical intervention, or aging—creates a "window of vulnerability" in the Central Nervous System (CNS). Without the regulatory oversight of 17 beta-estradiol (E2), the brain's innate immune system becomes hypersensitive, leading to the chronic neuroinflammation that characterizes Alzheimer's Disease and Multiple Sclerosis.

3.1 Alzheimer's Disease (AD): Beyond the Amyloid Cascade

While the "Amyloid Cascade Hypothesis" has dominated AD research for decades, recent shifts in neurobiology emphasize that amyloid-beta (A-beta) accumulation is exacerbated by a pro-inflammatory environment. Estrogen acts as a multi-modal defense against AD pathology by targeting both the production of toxic proteins and the brain's inflammatory response to them.

Non-Amyloidogenic Processing: Estrogen shifts the processing of Amyloid Precursor Protein (APP) toward the alpha-secretase pathway (the non-amyloidogenic route). By increasing the activity of enzymes like ADAM10, E2 promotes the production of soluble APP-alpha (sAPP-alpha), which is actually neuroprotective, while simultaneously reducing the production of the neurotoxic A-beta 1-42 peptides (Hansson et al., 2021).

Tau Pathology and Kinase Regulation: A hallmark of AD is the formation of neurofibrillary tangles composed of hyperphosphorylated Tau protein. Estrogen regulates the activity of GSK-3 beta (Glycogen Synthase Kinase-3 beta), the primary kinase responsible for Tau

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phosphorylation. By activating the PI3K/Akt pathway, E2 keeps GSK-3 beta in an inactive state, thereby preventing the structural collapse of the neuronal cytoskeleton.

The Bioenergetic Crisis: AD is often described as "Type 3 Diabetes" due to impaired glucose metabolism in the brain. Estrogen is a key regulator of the glucose transporter GLUT1 and mitochondrial enzymes like Cytochrome c Oxidase. The loss of estrogen during menopause leads to a "bioenergetic gap," where the brain struggles to meet its metabolic demands, triggering a compensatory inflammatory response that further damages neurons (Zarate et al., 2017).

3.2 Multiple Sclerosis (MS): The Pregnancy Paradox and Remission

Multiple Sclerosis is a chronic demyelinating disease driven by the infiltration of peripheral immune cells into the CNS. The "Pregnancy Paradox"—the observation that MS symptoms significantly decrease during the third trimester when estrogen levels are at their peak—provides the strongest clinical evidence for estrogen's neuroprotective role.

Blood-Brain Barrier (BBB) Stabilization: In MS, the primary insult is the breakdown of the BBB. Estrogen strengthens the tight junction proteins (such as Occludin and Claudin-5) between endothelial cells. This "seals" the barrier, preventing autoreactive T-cells and B-cells from migrating from the bloodstream into the brain parenchyma. This reduced infiltration significantly lowers the rate of new lesion formation (Miller et al., 2020).

Immunomodulation and Remyelination: Estrogen shifts the systemic immune profile from a pro-inflammatory Th1/Th17 response to an anti-inflammatory Th2 response. Within the CNS, E2 acts on oligodendrocyte precursor cells (OPCs) through ER beta. This promotes the maturation of OPCs into myelin-producing oligodendrocytes, directly aiding in the repair of damaged myelin sheaths (remyelination). Clinical trials using Estriol, a weaker estrogen dominant during pregnancy, have shown a reduction in brain atrophy and

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improved cognitive performance in MS patients, suggesting a viable adjunctive therapy (Miller et al., 2020).

Table 3. Cellular-Specific Mechanisms of Estrogen-Mediated Neuroprotection within the Neurovascular Unit.

Neurons	Up-regulation of Bcl-2; Ca^{2+} homeostasis	Reduced Apoptosis; Enhanced Memory
Microglia	Inhibition of NF-kappa B signaling	Reduced Pro-inflammatory cytokines
Astrocytes	Increased Glutamate Transporters (GLT-1)	Prevention of Excitotoxicity
Endothelium	Tight junction protein stabilization	BBB integrity; Reduced leukocyte infiltration

The table illustrates how estrogen provides comprehensive neuroprotection by targeting multiple cell types within the central nervous system. In neurons, it prevents cell death by upregulating anti-apoptotic proteins like Bcl-2, while in microglia, it quenches inflammation by inhibiting the NF-kappa B pathway. Additionally, it preserves synaptic health through astrocytic glutamate clearance and maintains the physical barrier of the brain by stabilizing endothelial tight junctions. This multi-cellular approach ensures that estrogen not only protects individual neurons but also maintains the structural and chemical integrity of the entire brain environment.

3.3 The "Timing Hypothesis": A Critical Caveat

An essential theme in modern neuro-endocrinology is the **Timing Hypothesis**. Evidence suggests that estrogen is highly protective when administered to "healthy" neurons or

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during the early stages of menopause. However, if the brain has been deprived of estrogen for a long period or is already burdened by heavy A beta plaques, the expression of Estrogen Receptors (ERs) decreases, and E2 may lose its protective efficacy or even become toxic. This underscores the importance of personalized, early-intervention hormonal strategies.

4. The "Timing Hypothesis" and Clinical Challenges

The translation of estrogen's neuroprotective potential from the bench to the bedside has been fraught with complexity, primarily due to the "Timing Hypothesis." This theory posits that the beneficial effects of Hormone Replacement Therapy (HRT) on brain health are strictly contingent upon the age and hormonal status of the woman at the time of treatment initiation.

4.1 The Legacy of the Women's Health Initiative (WHI)

In the early 2000s, the Women's Health Initiative (WHI) trials sent shockwaves through the medical community by reporting that combined HRT increased the risk of dementia in women over the age of 65. However, modern retrospective analyses have identified a significant methodological flaw: the average age of participants in the WHI was 63—nearly a decade past the onset of menopause.

Current research indicates that by this age, the brain has already undergone significant "estrogen-deprivation" changes, including the down-regulation of ER alpha and a shift in mitochondrial metabolism. In these older, estrogen-depleted brains, E2 may no longer act as a protectant; instead, it can exacerbate existing inflammatory pathways—a phenomenon often called the "Healthy Cell Bias of Estrogen Action" (Zimmer et al., 2024).

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4.2 The "Window of Opportunity"

The "Window of Opportunity" suggests that HRT must be initiated during the perimenopausal period or early menopause to be effective. During this critical period, neuronal receptors are still abundant and functional. When E2 is introduced early, it maintains the "M2" anti-inflammatory state of microglia and preserves white matter integrity.

A recent study by Zimmer et al. (2024) reinforces this, showing that women who began HRT within five years of menopause exhibited significantly lower levels of A-beta plaque accumulation compared to those who started treatment later. This suggests that estrogen acts as a preventative shield rather than a restorative cure for existing damage.

4.3 Clinical Challenges: Routes and Formulations

Beyond timing, the route of administration presents a major challenge. Oral estrogens undergo "first-pass metabolism" in the liver, which increases the risk of thromboembolism (blood clots). Conversely, transdermal estradiol (patches or gels) bypasses the liver and is associated with a much lower risk profile. Furthermore, the use of Selective Estrogen Receptor Modulators (SERMs)—which provide the benefits of estrogen in the brain without stimulating breast or uterine tissue—remains a frontier of active clinical investigation.

The future of estrogen therapy lies in "precision endocrinology." Rather than a one-size-fits-all approach, clinicians must consider the timing of initiation, the specific formulation, and the individual's baseline neuroinflammatory state. Moving forward, the goal is to target GPER and ERβ specifically to provide neuroprotection while avoiding the peripheral side effects associated with systemic ER alpha activation.

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5. Future Directions: SERMs and Brain-Selective Therapy

As the molecular mechanisms of estrogen become clearer, the focus of pharmaceutical research has shifted toward "precision estrogenics." The primary challenge of traditional 17 beta-estradiol (E2) therapy is its pleiotropic nature; while it is neuroprotective in the CNS, its activation of ER alpha in peripheral tissues can promote cellular proliferation in the breast and endometrium, potentially increasing oncogenic risks. To circumvent this, researchers are developing strategies to isolate the hormone's "good" effects from its "bad" ones.

5.1 Selective Estrogen Receptor Modulators (SERMs)

SERMs are "designer" ligands that exhibit tissue-specific activity. By inducing unique conformational changes in estrogen receptors, a SERM can act as an agonist in the brain (promoting neuroprotection) while acting as an antagonist in reproductive tissues.

Raloxifene, a second-generation SERM, has been a primary focus. While initially approved for osteoporosis, recent clinical data suggests it may stabilize cognitive decline in post-menopausal women with Alzheimer's by mimicking estrogen's anti-inflammatory effects in the hippocampus. However, as noted by Yousefi (2024), the "first-generation" SERMs often lack the full potency of E2 in the brain, leading to a search for "neuro-SERMs" specifically optimized for CNS penetration and ER-beta or GPER selectivity.

5.2 Brain-Targeted Delivery Systems and Prodrugs

Another innovative approach involves the use of brain-selective estrogen prodrugs. One promising candidate is 10,17 beta-dihydroxyestra-1,4-dien-3-one (DHED). This compound is biotransformed into active E2 only within the brain, thanks to specific enzymatic reactions that do not occur in the rest of the body. This approach effectively

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"bathes" the brain in protective estrogen while leaving the peripheral organs untouched (Li, 2025).

Furthermore, the use of **nanotechnology** to ferry estrogen across the Blood-Brain Barrier (BBB) is gaining traction. By encapsulating E2 in lipid nanoparticles or coating them with ligands that target endothelial transporters, researchers can achieve therapeutic concentrations in the CNS with much lower systemic doses, significantly reducing the risk of side effects.

5.3 Targeting the GPER Pathway

Because the membrane-bound GPER mediates many of the rapid, non-genomic anti-inflammatory effects of estrogen without the proliferative risks associated with nuclear ER-alpha, it has become a "hot" therapeutic target. Small-molecule GPER agonists are being tested for their ability to suppress microglial activation and protect dopaminergic neurons in Parkinson's models.

Table 4. Comparative Analysis of Current and Emerging Estrogen-Based Therapeutic Strategies for Neuroprotection.

17 beta-estradiol	Potent; activates all pathways	Systemic side effects (Cancer risk)	Hansson (2021)
SERMs (e.g., Raloxifene)	Tissue-specific; safer for long-term	Less potent neuroprotection	Yousefi (2024)
Brain-Targeted E2	Avoids peripheral metabolism	Delivery across BBB is complex	Li (2025)

The table No. 04 evaluates three primary therapeutic approaches designed to leverage estrogen's neuroprotective properties. While 17 beta-estradiol offers the most potent

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activation of all protective pathways, its clinical utility is hampered by systemic risks, including cancer. To mitigate this, SERMs provide a safer, tissue-specific alternative, though often with reduced efficacy in the CNS. The emerging field of Brain-Targeted E2 (such as prodrugs or nanocarriers) represents the most sophisticated strategy, aiming to maximize local concentration in the brain while bypassing peripheral side effects, despite the inherent challenges of crossing the blood-brain barrier.

6. Conclusion

Estrogen is a formidable ally in the fight against neuroinflammatory disorders, transcending its traditional role as a reproductive hormone to act as a sophisticated "master regulator" of the Central Nervous System. Its ability to simultaneously modulate microglial polarization, enhance mitochondrial bioenergetics, and stabilize synaptic connections makes it a unique multi-target therapeutic candidate in an era of complex poly-pathologies.

However, the clinical translation of these benefits requires a nuanced approach. Future research must prioritize the optimization of the "window of opportunity" to ensure interventions occur before irreversible receptor down-regulation. Furthermore, the development of next-generation brain-selective ligands, such as neuro-SERMs and CNS-targeted prodrugs, remains essential. These innovations promise to harness estrogen's potent neuroprotective power without compromising systemic safety, ultimately offering a personalized shield against the devastating progression of neurodegenerative and neuroinflammatory diseases.

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