https://doi.org/10.48047/AFJBS.7.7.2025.510-518

African Journal of Biological Sciences

Research Paper Open Access

The Concanavalin A-Induced Autoimmune Hepatitis Model in Mice: Historical Perspectives, Experimental Insights and Molecular Mechanisms

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Article History
Volume 7, Issue 7, July 2025
Received: 25 September 2025
Accepted: 22 July 2025
Published: 30 July 2025
doi:10.48047/AFJBS.7.7.2025.510-518

Abstract:

The Concanavalin A (Con-A)-induced autoimmune hepatitis (AIH) model is a well-established experimental tool for studying immune-mediated liver injury. This review provides a comprehensive overview of Con-A, including its biochemical properties, historical discovery, and evolution into a valuable research model. Initially identified as a plant lectin with specific carbohydrate-binding affinity, Con-A's hepatotropism and potent T-cell mitogenic effects enabled the development of an AIH mouse model that closely mimics the acute phase of human AIH. We summarize experimental considerations such as strain susceptibility, gender differences, dosing regimens, administration routes, and evaluation time points, emphasizing factors influencing reproducibility and severity. Furthermore, we explore the complex immunopathogenesis of Con-A-induced hepatitis, highlighting the roles of $CD4^+$ and $CD8^+$ T cells, Kupffer cells, natural killer cells, and associated cytokine networks. Key molecular mechanisms, including NF-κB activation, JAK/STAT signaling, and necroptotic pathways, are discussed in the context of hepatocellular injury. While the Con-A model offers advantages in cost-effectiveness and mechanistic insights, limitations such as its inability to replicate the chronicity and autoantibody profile of human AIH remain. Understanding these features supports its continued refinement and application in preclinical therapeutic research.

Keywords: Concanavalin A; Autoimmune hepatitis; Mouse model; Immunopathogenesis.

1. Chemical Composition and General Uses of Concanavalin A

Con-A is a plant lectin, a protein class that is characterized by their specific sugar-binding capabilities. Con-A's binding specificity is towards α-D-mannose and α-D-glucose moieties (Yu. Kostina et al., 2021). This carbohydrate-binding property has led to its widespread adoption in various biochemical and cellular applications, such as carbohydrate studies (Osada et al., 2024), glycoprotein purification (Othman et al., 2022), enzyme tagging (Wolpaw et al., 2022), cell membrane investigations (Huldani et al., 2022), cell agglutination (Cerdán-Alduán et al., 2025), and cell typing (Álvarez-Campos et al., 2024).

2. Historical background of Concanavalin A

The groundwork for discovering lectins and their actions was laid by the early observations by Stillmark in 1888 that ricin caused agglutination of red blood cells from various animals. This was later confirmed and expanded on by Landsteiner and Raubitschek in 1907 (Espino-Solis, 2015).

Con-A was first isolated as a crystalline protein from the jack bean (Canavalia ensiformis) by James B. Sumner in 1919. He called it Concanvalin A, as he had also isolated Concanavalin B and a third globulin that he called "canavalin" (Sumner, 1919). In 1936, Sumner and Howell further detailed the properties of Con-A, including its ability to agglutinate erythrocytes and yeast as well as to precipitate glycogen from solution. Importantly, they observed that the hemagglutination properties could be inhibited by sucrose and is dependent on bound Ca2+ and Mn2+ ions (Sumner and Howell, 1936). In 1938, the molecular weight of Con-A was elucidated to be 113,000 Da (Sumner et al., 1938).

The 1940s and 1950s saw further research into the precipitation (Abernethy and Avery, 1941), hemagglutination (Dameshek and Miller, 1943) and carbohydrate-binding (Cifonelli et al., 1956).

The 1960s and 1970s saw researchers conducted that further clarified the properties of Con-A. A study in 1969 noted the interaction of Con-A with transformed cells (whether by viruses, chemicals or radiation) but not normal cells, highlighting its role in studying membrane changes (Inbar and Sachs, 1969). In 1972, for example, the effect of pH was studied on the binding properties of Con-A. It was found that Con-A remained as a stable monomer with a molecular weight of 53000 in the pH range of 4.5-5.6. However, in a pH above 5.6, it forms a dimer with a molecular weight of ~100,000 and the carbohydrate-binding ligand α-D-methylmannopyranoside inhibits dimer formation at alkaline pH but has no effect at neutral pH (McKenzie et al., 1972). This period saw the emergence of research highlighting the role of Con-A as a mitogen (Powell and Leon, 1970).

The 1980s were pivotal for Con-A research as its role in immunological regulation was explored further. T-cells were highlighted to be the target of Con-A activation, highlighting its role as a T-cell mitogen (Dwyer and Johnson, 1981; Palacios, 1982; Lerner et al., 1989). Con-A was shown to have affinity towards the liver and hepatocytes (Takahashi and Kobayashi, 1982; Metcalf et al., 1987).

The 1990s saw the establishment of the Con-A-induced hepatitis model in experimental animals. The pivotal paper was published in 1992 and detailed how Con-A was capable of inducing T-cell mediated hepatitis in mice, evidenced by the resistance of SCID mice lacking T-cells and B-cells, and athymic nude mice, having only immature T-cells. In the study, strains tested were still limited, the dosages attempted were still in the trial stage and pharmacological interventions tried were only dexamethasone, cyclosporine A and FK 506 (Tiegs et al., 1992).

With the model having remarkable similarities to autoimmune hepatitis in humans, various studies attempted to further elucidate its pathogenic mechanisms, including the role of TNF-α (Gantner et

al., 1995), sinusoidal endothelial cells and Kupffer cells (Knolle et al., 1996), NK cells and IL-4 (Toyabe et al., 1997), IL-6 (Trautwein et al., 1998), and even the possibility of inducing fibrosis and inducing chronic hepatitis by repeatedly injecting Con-A (Kimura et al., 1999).

In the 2000s, reports were being made highlighting the potential of Con-A as an anti-cancer agent against hepatoma (Miyagi et al., 2004; Chang et al., 2007; Lei and Chang, 2009). Different dosages were attempted to determine the most effective in different strains in the Con-A hepatitis model (Xu et al., 2006). Importantly, the era of attempting therapeutic targets against the established Con-A hepatitis model was well-underway, with ME3738 reported to decrease NF-κB DNA binding and increase IL-6 expression and its STAT-3 downstream product (Klein et al., 2003) and JBP485 reported to decrease TNF-α, ICAM-1 and bcl-2/bax mRNA (Yang et al., 2009).

3. Experimental insights of the Con-A-induced hepatitis

The strain and gender of mice selected for the Con-A model influences the dosage required to achieve an effective result of induced hepatitis. Early studies found that strains that have a Th1-biased immune response such as C57BL/6 and C3H are highly susceptible and therefore require lower doses (15-20 mg/kg body weight) to induce hepatitis. Meanwhile, Th2-biased strains like BALB/c and outbred mice such as NMRI typically necessitate using higher doses (>30 mg/kg) to achieve similar results (Heyman et al., 2015). However, responses vary depending on the environment and dosage responses may differ significantly (Liu et al., 2022). Female Balb/c and male C57BL/6J were found to be the most susceptible and stable in response to Con-A when comparing three mouse strains: Balb/c, C57BL/6J and ICR mice (Song et al., 2025). Still, male mice have traditionally been recommended for the model due to less variability in outcomes. (Heyman et al., 2015).

The preferred route of administration of Con-A is the intravenous route in the tail vein most commonly (Pudgerd et al., 2025). The ages of mice used in the Con-A model range from 6 weeks to 12 weeks (Liu et al., 2021a; Nabekura et al., 2024). The weights of the mice in the model were in the 20-30 grams range (Ahmad and Kathem, 2021; Elazab and Hsu, 2024). Rats could also be used to study autoimmune hepatitis using Con-A-induced hepatitis, but there were fewer reports on their use, but C6orf120 gene was of particular importance, indicating the importance of macrophages, NK cells and JAK-STAT as well as the Fas/FasL signaling pathways (Wu et al., 2022; Wang et al., 2024). The dosage required to effectively induce hepatitis can range anywhere from 5-50 mg/kg body weight in mice (Nabekura et al., 2024).

The duration after the Con-A injection for hepatitis to be evident differed considerably amongst experiments. Some reports euthanized mice 10 hours after Con-A injections (Liu et al., 2021b), some after 12 hours (Liu et al., 2024) and others after 18 hours (Yang et al., 2024).

The benefit of the Con-A model is that it is easy, cheap, convenient and reproducible, with histological features (such as lymphocyte infiltration) and serological changes (e.g. high levels of transaminases) being quite similar to AIH patients. However, the model lacks the chronic nature of AIH as a disease as well as the presence of auto-antibodies (Hao et al., 2022; Liu et al., 2022).

3.6.4 Mechanistic insights into Con-A-induced hepatitis

The pathogenesis of the Con-A-induced hepatitis involves an interplay of immune and cellular mechanisms. Con-A activates inflammatory cells, causes necroptosis and triggers inflammatory signaling pathways, all of which ultimately lead to liver damage. Con-A binds to mannose receptors on Kupffer cells and sinusoidal endothelial cells, triggering the activation of CD4+ T helper cells (Th0) via TCR recognition of the MHC class II-Con-A complex. Th0 cells differentiate into pro-inflammatory subsets (Th1 and Th17), which secrete cytokines like TNF-α,

IFN-γ, and IL-17, which are injurious to hepatocytes and which activate NF-κB, which upregulates inflammatory genes and triggers a positive feedback loop via several pathways (Figure (6)) that further increases inflammation (Liu et al., 2022).

Moreover, Con-A activates NK cells and cytotoxic CD8+ T lymphocytes, which lead to hepatocyte apoptosis via the Fas/FasL pathway. Additionally, Con-A leads to the upregulation of Receptor-Interacting Protein Kinase 3 (RIPK3)- Mixed Lineage Kinase Domain-Like protein (MLKL) pathway. The RIPK-MLKL pathway further damages hepatocytes through necroptosis (Hao et al., 2022). Furthermore, JNK (c-Jun N-terminal kinase) is activated by Con-A via the TNF-α and Janus kinase/ signal transducer and activator of transcription (JAK/STAT) signaling (Zhao et al., 2024).

Necrosis of hepatocytes due to the various mechanisms leads to the release of mitochondrial damage-associated molecular patterns (DAMPs), such as mitochondrial DNA (mtDNA), from necrotic hepatocytes further exacerbates inflammation by activating neutrophils through the TLR9-p38 MAPK pathway, leading to the production of reactive ROS and pro-inflammatory mediators like IL-6 and TNF-α. Neutrophils are activated by mtDNA via TLR9, which further amplifies the inflammatory response (Liu et al., 2021b).

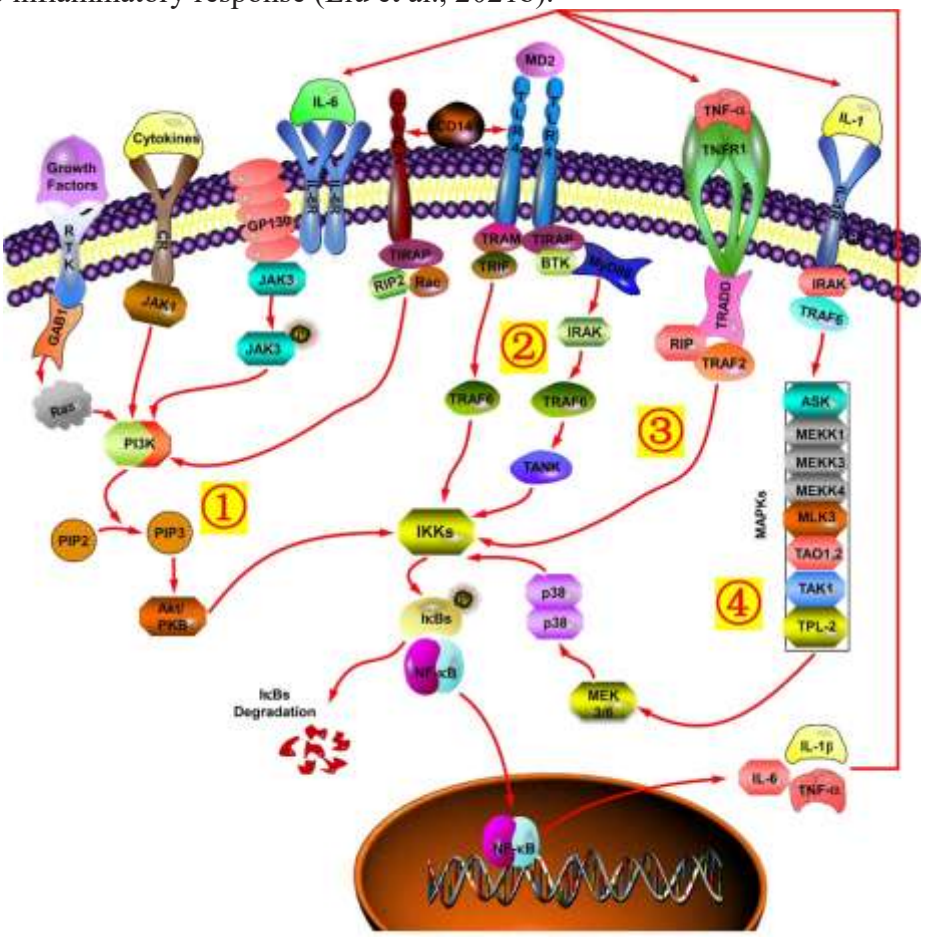

Figure (6): NF-κB-targeting signal transduction cascades play a crucial role in establishing the Con A-induced AIH mouse model. Various inflammatory mediators (including IL-1β, IL-6, TNF-α, and additional pro-inflammatory cytokines) can trigger IKK activation and promote the nuclear translocation of NF-κB dimers from the cytoplasmic compartment via several signaling cascades, encompassing the "TLR signaling pathway," "MAPK signaling pathway," and "PI3K/Akt signaling pathway." This nuclear migration of NF-κB ultimately leads to the coordinated

upregulation of numerous inflammatory and innate immunity genes, including IL-1β, IL-6, and TNF-α. Consequently, these cytokines (IL-1β, IL-6, TNF-α) together with NF-κB establish a positive feedback amplification circuit. The key pathways include: (1) PI3K/Akt signaling cascade, (2) TLR-2 and TLR-4 signaling pathways, (3) TNF-α signaling cascade, and (4) MAPK signaling pathway (Liu et al., 2022).

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