

In vivo and *in vitro* toxicological effects of *Aesculus hippocastanum* and its derivatives (horse chestnut): a systematic review

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Introduction: Horse chestnut (*Aesculus hippocastanum*) is traditionally used to alleviate chronic venous insufficiency symptoms due to its anti-edematous, anti-inflammatory, and venotonic properties. The main active ingredient, aescin, benefits patients with hemorrhoids or peripheral edema. However, studies on the toxicological safety of horse chestnut and its products are scarce. **Objective:** The aim of this systematic review was to summarize the current evidence on the toxicological evaluation of *Aesculus hippocastanum* and its derivatives in order to determine the safety of *in vitro* and *in vivo* use. **Materials and Methods:** This systematic review was conducted following the PRISMA 2020 recommendations. The study protocol was registered in the Open Science Framework Database, available at the following link: <https://osf.io/srdpe>. The electronic search was performed in five databases and grey literature. Studies that included animal models and *in vitro* techniques (Population) exposed to *Aesculus hippocastanum* and its derivatives (Exposure), and that reported an assessment of toxicological effects (Outcome), were included. Methodological quality was assessed using the ToxRTool. **Results:** From 465 identified studies, 12 were included according to the eligibility criteria. Of which, eight were *in vitro* studies. Six of these studies were considered "reliable without restriction" due to good methodological quality, while two *in vitro* studies were considered unreliable. Of the total of 12 studies included, five were *in vivo* studies. Only one was considered "reliable without restriction" with good methodological quality, while four were classified as "Not reliable." Most *in vivo* studies evaluated acute toxicity, with doses ranging from 1 to 6000 mg/kg. The most used *in vitro* method was MTT. **Conclusion:** We conclude that there is an urgent need for more robust studies, with better methodological descriptions and experimental rigor, to guarantee data reliability, especially *in vivo* data.

Palavras-chave: *Aesculus hippocastanum*; Horse chestnut; aescin.

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