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Update on Rhein Pharmacological Activities, Security, and Pharmacokinetics

Paul Grignard*

Department of pharmacology and pharmacokinetics education zombie

Corresponding author:
Paul Grignard

Department of pharmacology and pharmacokinetics education zombie

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Abstract

One of the primary active ingredients in rhubarb and Polygonum multiform is rhein, which is an anthraquinone molecule. Rhein has a wide range of pharmacological benefits, including effects that protect the heart and brain, hepatoprotect the liver, protect the kidneys, reduce inflammation, fight tumours, and control blood sugar. The system, which includes NF-B, PI3K/Akt/MAPK, p53, mitochondrial-mediated signalling pathway, oxidative stress signalling pathway, and others, is interconnected and complex. However, due to its weak water solubility and low bioavailability, its therapeutic applicability is rather constrained. Rhein may also be harmful to the liver and kidneys. Therefore, in order to serve as a guide for the creation and use of rhein, the pharmacological effects of rhein and its mechanism, pharmacokinetics, and safety investigations were examined in this work.

Rheum palmatum L., Cassia tora L., Polygonum multiform Thunb., and Aloe barbadensis Miller are just a few of the medicinal plants that contain the lipophilic anthraquinone Rhein (4, 5-dihydroxyanthraquinone-2-carboxylic acid), which has been used medicinally in China for more than a thousand years. The biological effects on human health are continuously being investigated. New research reveals that rhein has a wide range of pharmacological actions, including anti-inflammatory, antioxidant, anticancer, hepatoprotective, and antibacterial properties. The current review supports the prospective uses of rhein as a therapeutic agent by providing a thorough summary and analysis of its pharmacological properties.

Keywords: Rhein; Matrine; Cocrystal; Poor solubility; Pharmacokinetic; Molecular surface electrostatic potential

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Introduction

The anthrax quinone tricyclic aromatic compound Rhodin (4, 5-dihydroxyanthraquinone-2-carboxylic acid, C15H8O6), which has a molecular weight of 284.22, is soluble in alkaline solutions like pyridine and sodium bicarbonate aqueous solution but insoluble in water. It is possible to isolate Rhodin from a variety of traditional Chinese medicines, including cinnamon, rhubarb (Dahuang), Polygonum multiflorum (Heshouwu), and Polygonum cuspidatum. According to recent studies, Rhein has a number of beneficial effects, including those that are anti-inflammatory, anti-tumor, anti-diabetic, and hepatoprotective. Rhein may also be harmful to the liver and kidneys, according to certain reports. Additionally, Rhein has a low bioavailability because to its weak water solubility, which significantly hinders its clinical applicability. For this reason, it is crucial to understand the underlying dose-effect connection and change the structure to increase bioavailability and decrease toxicity. The pharmacological effects of Rhein and its derivatives have been outlined in a recent study, however they haven't been thoroughly explained, particularly the pertinent processes. In addition, little progress has been made in understanding the toxicity of Rhein. The pharmacological characteristics and possible mechanisms, pharmacokinetics, and toxicity of Rhein are all thoroughly discussed and analysed in this research, along with Rhein's prospective use prospects as a drug [1,2].

Plants have long been used as a source of medicine, particularly in developing nations where traditional cures must be used because modern medications are sometimes unavailable or too expensive. Since the late 1980s and up until the present, there has been a significant advancement in the study of herbal plants

as alternative medicinal agents for various ailments. In its tropical rainforest, Malaysia, a nation with a rich biodiversity, has been given access to important medicinal plant resources. Acanthaceae, which includes 250 genera and about 2500 species, is one of the most important families of dicotyledonous flowering plants. This family, which has many species with significant medicinal value, is primarily found in Indonesia, Malaysia, Africa, Brazil, and Central America. Currently, it is unclear how Rhein prevents the synthesis of proMMPs and the breakdown of proteoglycans. It has been suggested that diacerein may decrease collagenase expression in bovine articular chondrocytes by inhibiting the activator protein-1 activity, while the exact method of action of Rhein is unknown. On the other hand, it has been hypothesised that inhibiting ROS generation or lowering ROS levels lessens the IL-1-induced expression of collagenase in chondrocytes. Superoxide and NO generation are reported to be decreased by Rodin. All things considered, Rhein probably controls the proMMPs' synthesis and activity by obstructing a number of signalling pathways and thereby safeguards the cartilage. Rhine may have a direct protective effect on chondrocytes or a secondary effect by preventing the synthesis of proMMPs. Clarification of the role of Rhein-induced proMMPs reduction in proteoglycan breakdown requires additional research [3, 4].

Articular cartilage loss is a characteristic of osteoarthritis (OA). The primary components of the extracellular matrix of articular cartilage are collagen and proteoglycan aggregates. An altered articular chondrocyte metabolism results in the degradation of the cartilage matrix in the event of articular disorders like OA. No steroidal anti-inflammatory medications (NSAIDs), analgesics, and hyaluronan are now the main methods used in the clinical treatment of OA. These methods allow for symptomatic alleviation but do not appear to have any disease-modifying effects. In other cases, NSAIDs may even be harmful since they prevented the production of proteoglycan, which is essential for preserving cartilage function [5].

Therefore, it is imperative to create alternative agents that stop cartilage from being destroyed and/or encourage its healthy healing. Diacerein is currently being evaluated as a disease-modifying OA therapy in randomised placebo-controlled clinical trials of individuals with OA of the hip and knee. Diacerein has shown to be efficacious and well tolerated in the long-term treatment of OA. Animal models of OA, such as the accelerated canine model, have shown that diacerein is effective. Diacerein prevents the destruction of cartilage brought on by granulomas by lowering the levels of proinflammatory cytokines. The precise method which diacerein treat OA, nevertheless are unclear [6].

Preclinical and clinical drug development is a protracted and difficult procedure. The Kingdom of Saudi Arabia (KSA) is showing an increased interest in promoting indigenous content, research, and innovation, including clinical trials (Phase I-IV). Saudi Arabia now has more than 650 registered clinical trials, and this number is anticipated to rise. Making sure that medications are used safely and effectively is a crucial component of drug research and clinical trials. Because it focuses on the effects of medications in humans, clinical pharmacology is essential for helping decision makers make well-informed choices during the drug development process. Clinical pharmacology includes areas of study include pharmacokinetics, pharmacodynamics, and pharmacogenomics [7].

It is a developing field with numerous applications throughout all stages of drug development, such as choosing the best dosages for Phase I, II, and III studies, assessing bioequivalence and bio similarity research, and planning clinical investigations. Clinical pharmacology will be incorporated into research as well as regulatory bodies' requirements, which will enhance the drug development process and speed up the pipeline. Additionally, clinical pharmacology is used in hands-on patient care with the aim of individualised treatment. To optimise dosing for patients on an individual basis, techniques including therapeutic drug monitoring, pharmacogenomics, and model guided precision dosing are applied. Clinical pharmacology is an area of research that is underused in KSA; hence we think it's critical to educate the scientific community and healthcare workers [8].

Materials and Methods

After administering rhubarb decoction to the rats in the renal fibrosis model and the sham-operated group, the Rhein plasma content was measured using a sensitive and straightforward ultra-performance liquid chromatography-tandem triple quadrupole mass spectrometry (UPLC-MS/MS) method. Then, biomarkers of renal fibrosis in rat plasma were screened using the ultra-performance liquid chromatography-Micro mass quadrupole-time of flight mass spectrometry (UPLC-QTOF/MS) metabolomics technique. Additionally, the correlation between the concentrations of three biomarkers specifically linked to renal fibrosis and the plasma concentration of Rhein was examined [9].

Pharmacokinetic studies were initially used to examine the intestinal absorption of RD in the presence or absence of RH. Then, utilising the single-pass intestinal perfusion and Caco-2 cell models, the intestinal absorption of RD and RH was investigated. Utilising western blotting and the molecular docking approach finally. On a C18 column, chromatographic separation was completed with a 5-minute gradient elution. Multiple reaction monitoring (MRM) through an electrospray ionisation (ESI) source and operating in the negative ionisation mode were used to perform a tandem mass spectrometric detection.

Discussion

Many Chinese herbal remedies, including Heshouwu and Dahuang, which are frequently used in clinics, contain Rhodin. There are numerous pharmacological actions of Rhodin, and corresponding processes are intricately linked. It displays two-way reactions in the kidney and liver. The use of Rhein is also restricted to its structure. It is possible to increase the solubility and pharmacological targeting of Rhein derivatives by altering their phenolic hydroxyl or carboxyl group, which opens the door to future investigation [10].

Conclusion

The ability of Rhein to exhibit hepatoprotective, nephron protective, anti-inflammatory, antioxidant, anticancer, and antimicrobial activities has been convincingly demonstrated in various pharmacological studies in a number of in vitro and in

vivo models, as reviewed here, supporting the rationale behind several of its potential medicinal uses.

To investigate the hidden locations, though, more research must be conducted. Although several bioactivities of Rhein have been demonstrated in laboratory animals or cell models, it is still unclear what molecular pathways and targets are at play. This will prevent Rhein from being used in any additional clinical trials.

Conflict of Interests

None

Acknowledgments

None

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