DOI https://doi.org/10.5281/zenodo.10049652#222

TWIST, 2024, Vol. 19, Issue 3, pp. 219-221

TWIST

Journal homepage: www.twistjournal.net

Study on Acute Dermal Irritation of Mangiferin Hydrogel in Rabbits

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Abstract
The evaluation of the skin irritation potential of the new compound is essential to ensure the human's safety. In this study, the acute dermal irritation potential of Mangiferin hydrogel was investigated in rabbits following the Organization for Economic Cooperation and Development guidelines (OECD 404). During the skin irritation test, the Mangiferin hydrogel was applied to the rabbit skin, and the test site was monitored at different time intervals (1 hour, 4 hours, 24 hours, 72 hours, and thereafter for up to 14 days). Throughout the study, no dermal responses such as erythema or edema were observed. Based on these results, Mangiferin hydrogel does not produce any dermal irritation and appears to be safe for topical use.

Keywords
Mangiferin, Acute Dermal irritation, Rabbit

INTRODUCTION

Plant-based antioxidants are receiving significant attention for their ability to act as scavengers, protecting against the damaging impacts of oxidative stress. Mangiferin, a xanthone compound, is abundantly found in various parts of plants, including mango fruit components like the peel, stalks, leaves, barks, kernel, and stone, and has gained significant attention for its potent antioxidant properties [1]. Its C-glycosyl xanthone structure as shown in Fig 1(a), is primarily responsible for its anti-inflammatory effects, while is polyhydroxy components and glycosyl linkage contribute to its ability to scavenge free radicals [2]. Mangiferin's antioxidant activity increases significantly during pro-inflammatory and inflammatory conditions [3], making it a promising agent in the management of various diseases. Its anti-inflammatory effects are mediated by the modulation of various transcription factors, including NF-κB, Nrf-2, TNF-α and COX-2[4]. Beyond its antioxidant and anti-inflammatory properties, Mangiferin exhibits a wide range of health benefits, including anticancer, antiviral, antidiabetic, immunomodulatory, hepatoprotective, and analgesic effects [5] as shown in Fig 1(b). The anticancer potential of Mangiferin has been shown to suppress inflammation, oxidative stress, apoptosis, angiogenesis, and cell cycle pathways like PI3K/Akt [6]. However, despite its numerous advantages, the toxicological profile of Mangiferin is lacking. Hence it is crucial to thoroughly evaluate the toxicological effects of Mangiferin to predict for any potential side effects. For this purpose, the studies on acute dermal irritation was carried out on rabbits, as they are more sensitive to the chemicals [7]. The present study was conducted to evaluate the dermal irritations effects of Mangiferin hydrogel on rabbits following the OECD guidelines 404.

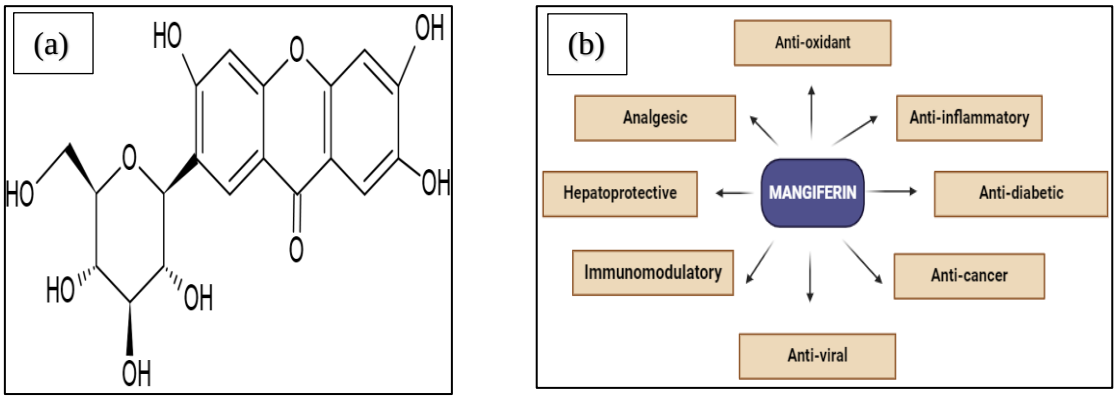

Fig. 1 (a) Structure of Mangiferin (b) Pharmacological effects of Mangiferin

MATERIALS AND METHODS

Mangiferin (CAS No. 4773-96-0) was purchased from the Chemical Centre in Mumbai with a purity level of 97%. Healthy Swiss Albino rabbits, 20 weeks old weighing between 4-5 kg, were collected from JSSCPO. The animals were kept in standard polycarbonate cages and maintained under laboratory conditions (22± 2°C, 12:12 light: dark cycle, 30-70% relative humidity) with access to normal pellet and water ad libitum. Before the initial application, the animals were given a 10-day period to acclimatize. The research conducted at JSS College of Pharmacy, Ooty was approved by the Institutional Animal Ethics Committee (1AEC) under approval number JSSCPO/OT/IAEC/38/2023-24.

Acute dermal irritation

The acute dermal irritation study was carried out as per OECD 404 (Acute dermal irritation/corrosion) [8]. The rabbits were grouped into a placebo control and a treatment group. The placebo control received plain carbapol gel; the treatment group was provided with Mangiferin hydrogel (10% contains 0.5g of Mangiferin). To prepare the Mangiferin hydrogel, the Mangiferin (0.5g) was dissolved in 0.1% DMSO along with the carbapol gel. Approximately (˜5cm×5cm) of the rabbit's trunk area was left without clipping for experimental purposes. Each rabbit had a 2.5 × 2.5 cm gauze patch applied with the test substance underneath, covered with an occlusive dressing. The test substance remained in contact with the skin for 4 hours before the removal of the dressings. Any residual substance was gently washed away with lukewarm water at the end of the exposure period prior to assessing dermal reactions. At 30 minutes, 1 hour, and 4 hours after removal of patches, no dermal responses were observed. To confirm the initial findings, the test was repeated with two additional rabbits. Concurrently, three additional studies involving repeated dermal applications were conducted over 7 consecutive days. The effect of Mangiferin hydrogel was evaluated on rabbit skin and scoring was given for erythema and edema at different intervals (1 hour, 4 hours, 24 hours, 72 hours) after application in the test sites. The scoring was given according to the OECD guidelines 404, from 0-4. 0: score for no reaction, 1: score for slight erythema or edema, 2: score for well-defined erythema or edema, 3: score for moderate, and 4: score for severe erythema or edema. The scores of each animal at different time points were combined and averaged to determine a mean irritation score. The scores were then compared to those of control rabbits. The average of these mean scores produced the primary irritation index [7, 9, 10].

RESULTS

Acute dermal irritation

The Mangiferin hydrogel-treated group showed no signs of toxicity and their body weight remained constant throughout the study. Furthermore, no erythema or edema was observed on the tested skin, it appeared to be normal (Fig 2). The results of the dermal irritation studies for single and repeated exposure are shown in Table 1.

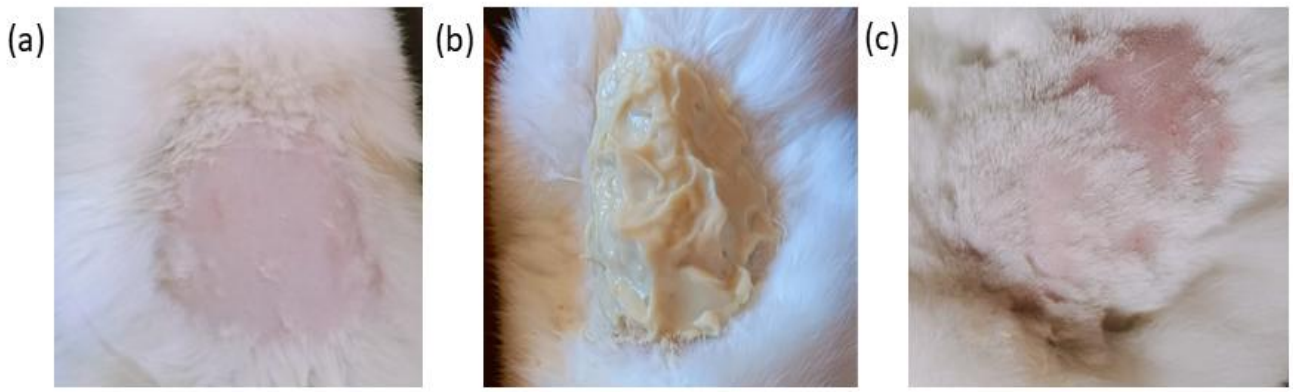

Fig 2: (a) Dermal irritation and skin sensitization test on rabbit **(b)** Before the application of the test compound Application of Mangiferin hydrogel **(c)** After 14 days of application

Table 1 Acute dermal irritation test of Mangiferin hydrogel at different time intervals

Mangiferin hydrogel	Dermal irritation	1 hour	24 hours	48 hours	72 hours
Dermal irritation of Mangiferin hydrogel at different time interval	Erythema Score	0	0	0	0
	Edema Score	0	0	0	0
	Erythema Score	0	0	0	0
	Edema Score	0	0	0	0

DISCUSSION

Mangiferin showcases a diverse array of health-promoting properties, encompassing anti-cancer, anti-viral, anti-diabetic, immunomodulatory, hepatoprotective, anti-oxidant, anti-inflammatory, and analgesic effects**.** Nevertheless, despite its copious benefits, the toxicological profile of Mangiferin remains lacking. The acute dermal irritation study is an important part of preclinical safety assessments for new chemicals before human exposure. This research was carried out to evaluate if Mangiferin hydrogel has any effects on the skin. The acute dermal irritation study showed that the hydrogel-treated rabbits had no dermal responses, such as erythema or edema. From the initial to the end of the study, no signs of toxicity were observed. Throughout the study, the body weight remained constant.

CONCLUSION

In this study, Mangiferin hydrogel did not cause any signs of toxicity up to 14 days. In the acute skin irritation study, no erythema or edema was observed. Therefore, the findings indicate that dermal application of Mangiferin hydrogel does not lead to any toxicological effects and it may be safe for use. Further chronic toxicity studies and animal studies will be continued for wound healing properties.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENT

We acknowledge the generous research infrastructure and support from the Department of Pharmacology. (DST-FIST, Sponsored) from JSS College of Pharmacy, JSS Academy of Higher Education and Research, Rocklands, Ooty, The Nilgiris, Tamil Nadu, India.

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