



Pharmacokinetics of Plant Derived miRNAs Following Intravenous Administration

Peiqi YAN ^{1,2} #, Yi LUO ^{1,2} #, Ling ZHAO ³, Fei SHI ³,
Mingzhou LI ^{1,2}, Anan JIANG ^{1,2} * & Xun WANG ^{1,2} *

¹ Institute of Animal Genetics and Breeding, College of Animal Science and Technology,
Sichuan Agricultural University, 211 Huimin Road, Chengdu 611130, China

² Farm Animal Genetic Resources Exploration and Innovation Key Laboratory of Sichuan Province,
Sichuan Agricultural University, 211 Huimin Road, Chengdu 611130, China

³ College of Veterinary Medicine, Sichuan Agricultural University,
211 Huimin Road, Chengdu 611130, China

SUMMARY. Since the research that plant miRNAs have potential to cross-regulate mammalian gene expression was reported, plant microRNAs provide another promising therapeutic approach for the treatment of mammalian diseases. However, there have been few detailed pharmacokinetic studies about plant miRNAs on animals. In this study, four synthetic plant miRNAs with 2'-o-methylated at the 3' end (miR164a-5p, miR166a-5p, miR167e-5p and miR319a-3p) were intravenous administered to Kunming mice as a mixture at the dose of 0.1645 and 1.6450 $\mu\text{g}/\text{kg}$, respectively. The concentration levels of individual miRNA in plasma were determined with stem-loop RT-PCR. The results indicated that the levels of most synthetic plant miRNAs rapidly decreased in addition to miR164a-5p after 5 min post injection. The pharmacokinetic parameters of miR164a-5p with two doses were calculated by two-compartmental analysis using DAS 2.0. The $\text{AUC}_{(0-t)}$ values in the plasma were 9.32 and 13.78 $\text{min}\cdot\text{mg}/\text{L}$, respectively. The plasma concentration at 5 min post injection with two doses were 0.18 and 0.62 $\mu\text{g}/\text{L}$, respectively.

RESUMEN. Dado que se informó sobre la investigación de que los miRNAs de plantas tienen potencial para regular de forma cruzada la expresión de genes de mamíferos, los microRNAs de plantas proporcionan otro enfoque terapéutico prometedor para el tratamiento de enfermedades de los mamíferos. Sin embargo, ha habido pocos estudios farmacocinéticos detallados sobre miRNAs de plantas en animales. En este estudio, cuatro miRNAs de plantas sintéticas con 2'-o-metilados en el extremo 3' (miR164a-5p, miR166a-5p, miR167e-5p y miR319a-3p) se administraron por vía intravenosa a ratones Kunming como una mezcla a la dosis de 0.1645 y 1.6450 $\mu\text{g}/\text{kg}$, respectivamente. Los niveles de concentración de miRNA individuales en plasma se determinaron con RT-PCR de tallo-bucle. Los resultados indicaron que los niveles de la mayoría de los miRNAs de plantas sintéticas disminuyeron rápidamente además de miR164a-5p después de 5 min de la inyección. Los parámetros farmacocinéticos de miR164a-5p con dos dosis se calcularon mediante análisis de dos compartimentos utilizando DAS 2.0. Los valores de $\text{AUC}_{(0-t)}$ en el plasma fueron 9.32 y 13.78 $\text{min}\cdot\text{mg}/\text{L}$, respectivamente. La concentración plasmática 5 min después de la inyección con dos dosis fue de 0.18 y 0.62 $\mu\text{g}/\text{L}$, respectivamente.

KEY WORDS: pharmacokinetic, plant derived miRNAs, stability.

These authors contributed equally to this work

* Authors to whom correspondence should be addressed. E-mails: ajiang@sicau.edu.cn (Anan Jiang); xunwang@sicau.edu.cn (Xun Wang).