

謝 誌

本論文承蒙恩師謝校長明村博士及藥學系主任劉主任正雄博士指導教誨與支持鼓勵，方得以順利完成，衷心感銘，永誌難忘。

研究期間承蒙陳所長忠川、藥理學科林文川教授、醫技系嚴以聖老師、藥學系謝文全副教授、張淑貞副教授、藥化所吳金濱副教授惠賜寶貴意見，本所闕甫副教授、吳啟瑞助理教授，以及邱年永技正在藥材鑑別上的幫助，動物中心王文信先生的協助，謹此致上由衷的謝忱。

感謝醫技系林玉鳳、顏昆山及吳岳文、隆德、裕仁學長、立偉、敏秀、偉德、佩如、威良、國清、恒璋、汎修、健源、俊杰、彥鈞、書銘、心霞、朝陽、仙如、佳惠、正賢、尚志、玉鈴、素琴、諸位學弟妹於研究過程中給予的協助，表達誠摯的謝意。

此外，謝謝父母的關心、家人的支持及先生的體貼照顧，謹銘記在心。

本論文由本校專題計畫：CMC88-CPS-05，CMC89-CPS-05 經費補助，在此一併誌謝。

目錄

謝誌	I
目錄	II
縮寫表	IV
圖目錄	VI
表目錄	VIII
中文摘要	1
英文摘要	4
第一章 緒論	6
1-1 枸杞子之文獻考察	8
1-1-1 枸杞子之本草學考察	
1-1-2 枸杞子之來源植物藥用植物學考察	
1-1-3 枸杞子之生藥學文獻考察	
1-1-4 枸杞子之成分考察	
1-1-5 枸杞子之藥理文獻考察	
1-2 東莨菪素之文獻回顧	33
1-2-1 東莨菪素的抽取及其物理、化學特性	
1-2-2 東莨菪素之藥理作用	
1-2-3 東莨菪素相關結構 coumarin (香豆素)類的 HPLC 研究	
1-3 研究背景及相關資料	37
1-3-1 藥物動力學	
1-3-2 血小板功能及其與血管壁相互作用的機轉	
1-3-3 血藥濃度與藥理效應	
1-4 研究目的	45
第二章 實驗材料與方法	46
2-1 實驗材料與設備	47
2-1-1 藥物動力學實驗	
2-1-2 血小板聚集性抑制實驗	
2-2 實驗方法	50
2-2-1 溶液製備	
2-2-2 東莨菪素血漿檢品之 HPLC 定量分析方法	
2-2-3 血小板聚集性測定法 - 比濁法	

2-2-4 藥效與藥理學模型

第三章	東莨菪素家兔血漿檢品之 HPLC 分析	59
第四章	東莨菪素家兔之藥物動力學	73
4-1	東莨菪素家兔靜脈注射後之藥物動力學研究	74
4-2	東莨菪素家兔口服給藥後之藥物動力學研究	79
4-3	東莨菪素家兔肌肉注射給藥後之藥物動力學研究	85
第五章	東莨菪素與枸杞子氯仿層抽出物之血小板聚集性抑制作用	90
5-1	東莨菪素血小板聚集性抑制之研究	91
5-2	枸杞子氯仿層抽出物血小板聚集性抑制之研究	101
第六章	東莨菪素與枸杞子氯仿層抽出物對家兔血小板聚集性抑制作用之藥效學研究	108
6-1	東莨菪素對家兔血小板聚集性抑制作用之藥效學研究	109
6-2	枸杞子氯仿層抽出物對家兔血小板聚集性抑制作用之藥效學研究	125
第七章	結論、新發現與展望	134
7-1	結論	
7-2	新發現	
7-3	展望	
第八章	參考文獻	139

Abbreviations

α : distribution rate constant

β : elimination rate constant

A: the zero time intercept associated with the alpha phase

AA: arachidonic acid

ADP: adenosine 5'-diphosphate

AUC: Area under the plasma level-time curve

AUMC: area under the (first) moment versus time curve

B: the zero time intercept associated with the beta phase

C.V.: coefficients of variences

cAMP: cyclic adenosine monophosphate

Cl/F: clearance divide by the bioavailability

CL: clearance

C_{max} : the peak concentration

CO: cyclooxygenase

Coll: collagen

C_p : concentration of drug in plasma

e: intercept

F: bioavailability

k_{10} : elimination rate constant from central compartment

k_{12} : distribution rate constant for transfer of drug from central to peripheral compartment

k_{21} : distribution rate constant for transfer of drug from peripheral to central compartment

k_a : absorption rate constant

k_a -HL: absorption half-life

LB: *Lycium barbarum* LINNAEUS

LBC: chloroform extract of LB

LOD: Limit of detection

LOQ: Limit of quantitation

MRT: mean residence time

NE: norepinephrine

PD: pharmacodynamics

PGI₂: prostagland I₂

PK: pharmacokinetics

PPP: platelet poor plasma

PRP: platelet rich plasma

S: slope

Scop: scopletin

$t_{1/2\alpha}$: distribution half-life

$t_{1/2\beta}$: elimination half-life

t_{\max} : the time of peak concentration

TXA₂: thromboxane A₂

V_1/F : apparent volume of distribution of the central compartment divide
by the bioavailability

圖目錄

Fig. 1. 枸杞之本草系統圖	10
Fig. 2. The chemical structure of scopoletin.	36
Fig. 3. Chromatograms of scopoletin in rabbits plasma.	62
Fig. 4. The standard curve of scopoletin (0.01-1 μ g/mL) in rabbits plasma.	63
Fig. 5. The standard curve of scopoletin (1-100 μ g/mL) in rabbits plasma.	64
Fig. 6. Stability of scopoletin in rabbit plasma at 37 $^{\circ}$ C.	65
Fig. 7. Stability of scopoletin in rabbit plasma at -30 $^{\circ}$ C.	66
Fig. 8. Mean plasma concentration-time profiles of scopoletin (2, 10 or 50 mg/kg, i.v.) in rabbits.	77
Fig. 9. Mean plasma concentration-time profiles of scopoletin (50, 100, or 250 mg/kg, p.o.) in rabbits.	83
Fig. 10. Mean plasma concentration-time profiles of scopoletin (50 mg/kg, i.m.) in rabbits.	88
Fig. 11. Maximal intensity and velocity of platelet aggregation induced by 10 μ M ADP, 500 μ g/mL AA and 10 μ g/mL collagen in rabbit.	96
Fig. 12. Maximal intensity and velocity of platelet aggregation induced by 10 μ M ADP, 500 μ g/mL AA and 10 μ g/mL collagen in rabbit at 5 min after scopoletin (50 mg/kg, i.v.).	97
Fig. 13. Maximal intensity and velocity of platelet aggregation induced by 10 μ M ADP, 500 μ g/mL AA and 10 μ g/mL collagen in rabbit at 30 min after scopoletin (250 mg/kg, p.o.).	98
Fig. 14. Maximal intensity and velocity of platelet aggregation induced by 10 μ M ADP, 500 μ g/mL AA and 10 μ g/mL collagen in rabbit at 30 min after chloroform extract of <i>Lycium barbarum</i> (250 mg/kg, p.o.).	105
Fig. 15. Time and mean plasma concentration versus inhibitory effect profile, respectively. The inhibitory effect of platelet aggregation induced by ADP, AA and collagen after	

- intravenous bolus injection scopoletin (2 mg/kg) in rabbits. 116
- Fig. 16. Time and mean plasma concentration versus inhibitory effect profile, respectively. The inhibitory effect of platelet aggregation induced by ADP, AA and collagen after intravenous bolus injection scopoletin (10 mg/kg) in rabbits. 117
- Fig. 17. Time and mean plasma concentration versus inhibitory effect profile, respectively. The inhibitory effect of platelet aggregation induced by ADP, AA and collagen after bolus intravenous injection scopoletin (50 mg/kg) in rabbits. 118
- Fig. 18. Time and mean plasma concentration versus inhibitory effect profile, respectively. The inhibitory effect of platelet aggregation induced by ADP, AA and collagen after oral administration scopoletin (50 mg/kg) in rabbits. 119
- Fig. 19. Time and mean plasma concentration versus inhibitory effect profile, respectively. The inhibitory effect of platelet aggregation induced by ADP, AA and collagen after oral administration scopoletin (100 mg/kg) in rabbits. 120
- Fig. 20. Time and mean plasma concentration versus inhibitory effect profile, respectively. The inhibitory effect of platelet aggregation induced by ADP, AA and collagen after oral administration scopoletin (250 mg/kg) in rabbits. 121
- Fig. 21. Time and mean plasma concentration versus inhibitory effect profile, respectively. The inhibitory effect of platelet aggregation induced by ADP, AA and collagen after oral administration chloroform extract of *Lycium barbarum* LINNAEUS (50 mg/kg) in rabbits. 129
- Fig. 22. Time and mean plasma concentration versus inhibitory effect profile, respectively. The inhibitory effect of platelet aggregation induced by ADP, AA and collagen after oral administration chloroform extract of *Lycium barbarum* LINNAEUS (100 mg/kg) in rabbits. 130
- Fig. 23. Time and mean plasma concentration versus inhibitory effect profile, respectively. The inhibitory effect of platelet aggregation induced by ADP, AA and collagen after oral administration chloroform extract of *Lycium barbarum* LINNAEUS (250 mg/kg) in rabbits. 131

表目錄

Table 1. 東莨菪素標準濃度血漿檢品溶液之製備	53
Table 2. Limit of quantitation test for scopoletin in rabbit plasma.	67
Table 3. Recovery test of scopoletin in rabbit plasma.	68
Table 4. Intraday precision for scopoletin determination in rabbit Plasma.	69
Table 5. Interday precision for scopoletin determination in rabbit plasma.	70
Table 6. Stability of scopoletin in rabbit plasma at 37 .	71
Table 7. Stability of scopoletin in rabbit plasma at -30 .	72
Table 8. Pharmacokinetic parameters of scopoletin in rabbits after bolus intravenous injection.	78
Table 9. Pharmacokinetic parameters of scopoletin in rabbits after oral administration.	84
Table 10. Pharmacokinetic parameters of scopoletin in rabbits after intramuscular administration.	89
Table 11. Effect of scopoletin bolus intravenous injection on rabbits platelet aggregation induced by ADP, AA and collagen.	99
Table 12. Effect of scopoletin oral administration on rabbits platelet aggregation induced by ADP, AA and collagen.	100
Table 13. The number of platelets in PRP after 5 minutes of various drugs administration.	106
Table 14. Effect of <i>Lycium barbarum</i> chloroform extract oral administration on rabbits platelet aggregation induced by ADP, AA and collagen.	107
Table 15. Slope and intercept of log-linear model in inhibitory effect of platelet aggregation induced by ADP, AA and collagen with log Cp of scopoletin on rabbits after bolus intravenous injection application.	122
Table 16. Slope and intercept of log-linear model in inhibitory effect of platelet aggregation induced by ADP, AA and collagen with log Cp of scopoletin on rabbits after oral	

administration.	123
Table 17. The effects on half-life, elimination rate and dose retained with time after application of scopoletin in rabbits.	124
Table 18. Slope and intercept of log-linear model in inhibitory effect of platelet aggregation induced by ADP, AA and collagen-log Cp of <i>Lycium barbarum</i> chloroform extract on rabbits after oral administration.	132
Table 19. The effects on half-life, elimination rate and dose retained with time after oral administration of scopoletin or <i>Lycium barbarum</i> chloroform extract on rabbits.	133