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活血化瘀中草藥之生物活性評估

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天然藥物在世界各國幾千年來，曾被用來作爲傳統醫學之主要治療藥物；而中藥的使用在台灣、中國及華人社會相當普遍，然而我們對中藥之療效很少以現代醫學研究之方法給予有系統的評估其藥效；尤其對中藥之藥理作用機轉，有效成分之分析等更應有深入之探討。基於學術研究本土化之理念，十多年前（1987 年）我們在台大醫學院藥理學研究所曾組成小規模之中草藥藥效評估研究群，並與國內十多位生藥、化學家合作，進行有關「活血化瘀」中草藥成分之生物活性分析。所謂「活血化瘀」，若以現代醫學之闡釋，應爲：改善血液循環（improving circulation）、去除或防止血栓（antithrombotic）之意。

首先我們必須決定中草藥藥效評估之方法。一般而言藥理測試有體外試驗及活體動物試驗。體外試驗包括藥物對酵素、受體、細胞、組織、器官等各種生化、生理功能之測試；而活體動物試驗則包括使用清醒、麻醉動物及各種疾病動物模型之藥效評估。爲了中草藥之研究必須現代化與國際化，我們採用在西藥研發時常使用之藥理活性篩選方式；即先以離体組織或細胞來分析藥物之作用，有作用者再進行活體動物之藥效評估。因此，科內同仁蘇銘嘉教授進行中草藥對心臟功能之藥效評估，而我們實驗室則評估中草藥對血小板及血管功能等之影響。由此開始漸漸地研究領域擴展到氣管鬆弛、前列腺組織放鬆、抗氧化、自由基清除、消炎和細胞增生之藥理作用測試。如此以藥理活性爲依據，由植物萃取、分離、到純化，一步步篩選出具有生物活性之成分。這些研究結果顯示中草藥的確含有相當多之生物活性成分，值得進一步之研發。以下敘述部份研究成果，以提供各界參考。

一、影響血小板凝集之活性成分

血小板功能之藥效評估是相當簡單而容易之一種生物活性篩選模式。利用各種不同之血小板致活劑，可經由各種受體、訊息傳遞而引起血小板之凝集與釋放反應（如 ATP, 5-HT 等）（圖 1）。經此藥理活性分析，由天然物中可發現許多對血小板功能有影響之成分，若依其作用機轉之不同，可將這些抗血小板凝集成分歸納爲下列八類：1) PAF 受體拮抗成分，2) 膠原（collagen）受體拮抗成分，3) Thromboxane A_2 受體拮抗成分，4) ADP 受體活化成分，5) Phosphoinositide 分解抑制成分，6) Thromboxane A_2 生合成抑制成分，7) 增加 cAMP 之成分，8) Protein kinase C 活化成分等。幾種具有抗血小板凝集之成分在血栓模式之活體動物

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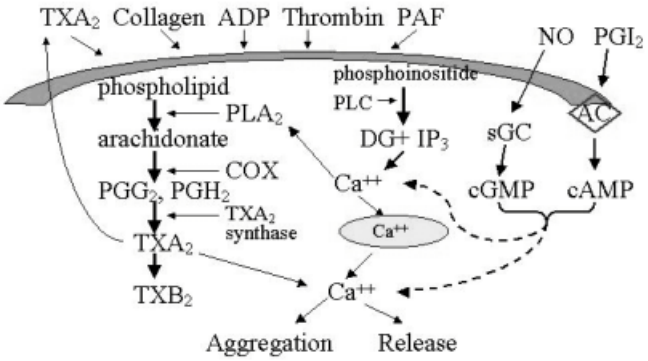

圖 1：血小板凝集與釋放反應相關之訊息傳遞

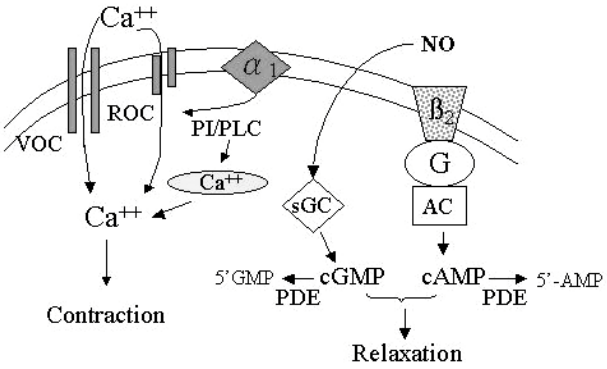

圖 2：血管平滑肌收縮與放鬆相關之訊息傳遞

亦得到證明有抗凝血作用。由這些對血小板凝集抑制成分之作用機轉，亦可以判斷其可能之其他生物活性與對何種組織或器官會產生藥理作用。例如對 thromboxane A_2、PAF 受體有抑制者，我們亦進行對血管、平滑肌氣管之藥理作用探討。

二、影響血管平滑肌收縮之活性成分

在有關血管之功能性評估中，我們選擇大鼠主動脈血管之平滑肌進行篩選。以 phenylephrine 及高鉀引發血管收縮，我們發現中草藥成分對血管之影響，依作用機轉之不同，可分爲下列五類：1) α_1-腎上腺受體拮抗成分，2) Thromboxane A_2 受體拮抗成分，3) 內皮細胞放鬆因子（EDRF）釋放成分，4) 鈣離子通道拮抗成分，5）血管收縮之鈣離子通道活化成分（圖 2）。前四項均可抑制血管之收縮反應或產生平滑肌之放鬆作用，而後者則可造成血管及其他平滑肌之收縮，是一種新的 voltage-dependent Ca^{2+} channel agonist。

三、氣管平滑肌鬆弛活性成分

我們以離体天竺鼠氣管平滑肌爲篩選模式，而發現天然物成分可經由下列之機轉而使氣管平滑肌放鬆：1) 鈣離子通道拮抗，2) Thromboxane A_2 受體拮抗，3) PAF 受體拮抗，4) M_3 膽鹼受體拮抗，5) β_2 腎上腺受體活化，及 6) Phosphodiesterase 抑制等作用。在 PAF 受体拮抗成分中，我們曾詳細研究 CIS-19 對氣管痙

攣活体動物之影響，並發現其可抑制發炎細胞之聚集、血漿之滲漏、氣管之痙攣等氣喘相關變化之作用，值得進一步繼續研發。

四、前列腺組織鬆弛活性成分

前列腺組織頗類似血管平滑肌，具有α_1 腎上腺受体，在交感神經興奮下，亦會有收縮作用。我們採用人類良性前列腺肥大（benign prostate hyperplasia, BPH）病人之組織，並以 phenylephrine 刺激α_1-腎上腺受體造成平滑肌收縮之實驗，來篩選α_1-腎上腺受體拮抗成分。爲了區分α_1 受体亞型，我們亦評估天然藥物成分對輸精管（α_{1A}），脾臟（α_{1B}）及血管（α_{1D}）來判斷它們是否具有選擇性，結果發現這些成分對受体亞型作用之差異性不大。

五、影響心肌收縮之活性成分

大部分天然物對心臟功能之作用評估多在蘇銘嘉教授之實驗室進行，並分析是否具有增強心肌收縮之作用，及抑制各種離子管道之活性，以找尋抗心率不整之藥效成分。我們實驗室亦曾發現一種活化鈣離子管道之致活劑 thaliporphine，對心肌、血管均具有加強收縮之效果。另外，我們亦曾在國科會之支援下進行一件產學合作計畫，由台灣雅楠植物作爲中間体原料，以合成一具有抗心率不整之新藥 STL-1。雖然該全新化合物比現有抗心率不整之藥物具有優點，但由於生体可用率不佳，此新藥之研發有待更進一步之改善。

六、抗氧化、自由基清除成分

對 thromboxane A_2 生合成具有抑制之抗血小板凝集成分，我們更進一步分析其作用機轉到底是抑制 cyclooxygenase 或 thromboxane A_2 synthase 而來。若屬於前者，即所謂抑制前列腺素合成之藥物，他們一般非常高比率是靠抑制花生四烯酸（arachidonic acid）之氧化反應。因此在抗氧化、自由基清除活性篩選試驗亦多具有相當之效果。事實上，中草藥大多數在体外試驗，甚或無細胞之純化學反應中即會呈現抗氧化、自由基清除之活性，但必須在活体動物体內再証明其具有活性才有應用可能性；而且往往不同動物模式，其藥效亦不見得相同。

七、抗發炎作用成分

有些抗血小板凝集之成分對發炎細胞之活性亦有抑制作用，特別在中性白球、肥大細胞，天然物成分可以抑制其去顆粒化作用、凝集作用、及減少過氧化物之產生。有些成分在活體動物實驗中亦可觀察到消炎、消腫之效果。這些作用有的是因抑制 lipoxygenase 之酵素活性，有些機轉則尚不清楚，需要再進一步之實驗評估。

八、抗細胞增生成分

爲了探討藥物對細胞生長（proliferation）及細胞凋亡（apoptosis）之影響，我們亦選用血管內皮細胞、

表 1　具生物活性之天然物成分

藥理作用	發表年代	成　　分	植物來源
一、抑制血小板凝集作用			
1. PAF 受體拮抗成分	1990	denudatin B	辛夷 (*Magnolia fargesii*)
	1992	aglafoline	大葉樹蘭 (*Aglaia elliptifolia*)
	1992	ochotensimine N-oxide	疏花黃堇 (*Corydalis ochotenisis*)
	1995, 1997	CIS-19, devir. of fagaronine	(*Fagara zanthoxyloides*)
	1996	khellactone deriv	日本前胡 (*Peucedanum japconica*)
	1997	bakkenolide G	山菊 (*Petasites formosanus*)
2. Collagen 受體拮抗成分	1993	frangulin B	台灣鼠李 (*Rhamnus formosana*)
	1993	avicine pseudocyanide	冀柄花椒 (*Zanthoxylum formosana*)
3. Thromboxane A_2 受體拮抗成分	1994	cinnamophilin	菲律賓樟樹 (*Cinnamomum philippinense*)
4. ADP 受體活化成分	1997	rugosin E	小飛陽草 (*Rosa rugosa*)
5. Phosphoinositides 分解抑制成分	1989	osthole	獨活 (*Angelica pubescens*)
	1989	protopine	延胡索 (*Corydalis* tubers)
	1989	xanthone deriv.	龍膽科 (Gentianaceae sp.)
	1990	chelerythrine 刺花椒 (*Zanthoxylum simulans*)	
	1992	xanthoxyletin, xanthyletin	柚根 (*Citrus grandis*)
	1992	poncitrin	枳殼 (*Poncirus trifoliata*)
	1992	suberosin	柚根 (*Citrus grandis*)
	1992	Aurapten 酒餅勒 (*Serverinia huxifolia*)	
	1995	shikonin	紫草 (*Arnebia euchroma*)
6. Thromboxane A_2 生合成抑制成分	1984	capsaicin	番辣椒 (*Capsicum* sp.)
	1987	butylidenephthalide	川芎 (*Ligusticum wallichii*)
	1988	apigenin	芹菜 (*Apium graveolens*)
	1988, 1991	quercetin, kaempferol, eugenol, gingerol, paeonol 等	
	1988	honokiol, magnolol	厚朴 (*Magnolia officinalis*)
	1989, 1990	ginsenosides, panaxynol	人參 (*Panax ginseng*)
	1990	dehydrokawain	月桃 (*Alpinia speciosa*)
	1992	trans-resveratrol	台灣鼠李 (*Veratrum formosanum*)
	1994	clausine-D	過山香 (*Clausena excavata*)
	1995	zingerol	薑 (*Zingiber officinalis*)
7. cAMP 增加成分	1992	Dicentrine	大香葉樹 (*Lindera megaphylla*)
	1994	girinimbine	山黃皮 (*Murraya euchrestifolia*)
8. Protein kinase C 活化成分 1993	Daphnoretin		南嶺蕘花 (*Wikstroemia indica*)

二、血管鬆弛作用			
1. α_1-腎上腺受體拮抗成分	1991-1995	dicentrine	大香葉樹 (*Lindera megaphylla*)
	1993, 1994	discretamine	白葉瓜馥木 (*Fissistigma glaucescens*)
	1994	N-allylsecoboldine	樟科植物成分之衍生物
	1995	N-methylactinodaphnine	呂宋青藤 (*Illigera luzonensis*)
	1996	govadine	罌粟科植物 (*Corydalis govaniane*)
	1996	tetrahydroxyprotoberberine, xylopine deriv. of *Xylopia discreta*	
	1997	ocoteine	無根藤 (*Cassytha filiformis*)
2. Thromboxane A_2 受體拮抗成分	1994	cinnamophilin	菲律賓樟樹 (*Cinnamomum philippinense*)
3. EDRF 釋放成分	1990	magnolol	厚朴 (*Magnolia officinalis*)
4. 鈣離子通管拮抗成分	1990	denudatin B	辛夷 (*Magnolia fargesii*)
	1990	fargesone B	辛夷 (*Magnolia fargesii*)
	1991	apigenin	芹菜 (*Apium graveolens*)
	1991	xanthone deriv.	龍膽科 (Gentianaceae sp.)
	1992	dictamine, fraxinellone	白鮮皮 (*Dictamnus dasycarpus*)
	1992	osthole	獨活 (Angelica pubescens)
	1992	protopine	延胡索 (*Corydalis tubers*)
	1992	xanthyletin	柚根 (*Citrus grandis*)
	1993	crychine	厚殼桂 (*Cryptocarya chinensis*)
	1994	14-acetoxycedrol	山柏 (*Juniperus squamata*)
	1994	laurotetanine	胡椒 (*Litsea cubeba*)
	2001	chalcones	
5. 鈣離子通道活化成分	1993, 1994	thaliporphine	芸香科植物 (*Neolitsea konishii*)
三、氣管擴張作用			
1. PAF 受體拮抗成分	1992	aglafoline	大葉樹蘭 (*Aglaia elliptifolia*)
	1993, 1995 1996	CIS-19, deriv of fagaronine	(*Fagara zanthoxyloides*)
2. M_3 受體拮抗成分	1994	Liriodenine	白葉瓜馥木 (*Fissistigma glaucescens*)
3. β2 受體活化成分	1996	BDTI, deriv. of higenamine	附子 (*Aconitium carmichealis*)
4. Phosphodiesterase 抑制成分	1993	atherosperminine	白葉瓜馥木 (*Fissistigma glaucescens*)
	1994	Osthole	獨活 (*Corydalis* tubers)
5. Thromboxane A_2 受體拮抗成分	1994	cinnamophilin	菲律賓樟樹 (*Cinnamomun philippinense*)
	1998	Khellactone deriv.	日本前胡 (*Peucedanum japonica*)
四、前列腺鬆弛作用			
α_1-腎上腺體拮抗成分	1997	Dicentrine	大香葉樹 (*Lindera megaphylla*)
	1999	N-methylactinodaphnine	呂宋青藤 (*Illigera luzonensis*)
	discretamine		白葉瓜馥木

			(*Fissistigma glaucescens*)
		govadine	罌栗科植物 (*Corydalis govaniane*)
		N-allylsecoboldine	樟科植物成分之衍生物
		Tetrahydroxyproto berberine xylopine driv. of *Xylopia discreta*	
五、影響心肌收縮作用			
	1993, 1994	thaliporphine	芸香科植物 (Neolitsea konishii)
	1994	dicentrine	大香葉樹 (Lindera megaphylla)
	1994	N-allylsecoboldine	樟科植物成分之衍生物
	1997	cinnamophilin	菲律賓樟樹 (Cinnamomum philippinense)
六、抗氧化、自由基清除作用			
	1994	magnolol, honokiol	厚朴 (*Magnolia officinalis*)
	1995	marchantinquinone	地錢 (Reboulia hemisphaerica)
	1996	N-allylsecoboldine deriv. of boldine	(樟科植物)
	1996	Isotorachrysone	中原氏鼠李 (Rhamnus nakaharai)
	1997, 2001	cinnamophilin	菲律賓樟樹 (Cinnamomun philippinense)
	1997	isoorientin-6′-O-glucoside	阿里山龍膽 (Gentiana arisanensis)
	1998	Butein	降香檀 (Dalbergia odorifera)
	2001	broussochalcone	Broussonetia papyriffera
七、抗發炎作用			
	1992	curcumin	薑黃 (*Curcuma longa*)
	1992, 1993	magnolol	厚朴 (*Magnolia officinalis*)
	1994	Norathyriol	龍膽科 (*Tripterosperoum lanceolatum*)
	2002	oxygenated xantones	連翹 (*Hypericum geminiflorum*)
八、抗血管平滑肌增生作用			
	1993, 2003	esculetin	茵陳 (*Artemisia scoparia*)
	1994	baicalein	黃芩 (*Scutellaria baicallensis*)
	1996	osthole	獨活 (*Corydalis* tubers)
九、降血脂作用			
	1993	dicentrine	大香葉樹 (*Lindera megaphylla*)
十、抗凝血作用			
	1991	6-pentadecylsalicylic acid	埔鹽 (*Rhaus semialata roxburghii*)
		F-11	刺花椒 (*Zanthoxylum simulans*)

平滑肌、前列腺、巨噬細胞、中性白血球、肝細胞等之初代細胞或相關之細胞株來研究藥物之影響，這些是目前實驗室之重點研究項目，並正持續進行中。

由上述體外試驗所篩選到具有生物活性之成分，理應都要再進一步測試對活體動物之藥理作用，以觀察是否具有研發價值。然而，上述具有活体外作用之藥物仍然很多未作此評估，原因在於能取得的量不足夠進行活体動物之實驗，有些在研發中發現作用強度不足以在活体動物呈現藥效。此外，動物體外有效之成分，往往會因生體可用率低、半衰期短、血漿蛋白結合力高、治療指數低，而在活體動物模式中發現藥效不佳或沒有作用。當然，中草藥之藥效可能由幾種不同成分之協同作用也是必須考慮之可能性。但是這些中草藥成分的確可以作爲新先導藥物（new leads），並可化學修飾方法來進行藥物之最佳化（optimization），以研發新的化合物（new chemical entity）。

過去十多年來我們所篩選過之天然物成分及粗分劃之樣品達數千個，具有藥理活性，且化學構造確定之純物質者列於表 1，提供有意繼續研發者參考。

致　　謝

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BIOLOGICALLY ACTIVE AGENTS ISOLATED FROM CHINESE HERBS AND MEDICINAL PLANTS

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Herbal plants have been used as important remedies in traditional medicines in many countries for hundreds of years. In oriental countries, some medicinal plants, so-called "vasoactive-thrombolytic" drugs have been claimed for the treatment of patients to improve circulation, induce fibrinolysis or prevent thrombosis. In order to modernize and develop scientifically Chinese herbal medicine, we have cooperated with chemists in large-scale pharmacological screening of many components isolated from Chinese herbs or medicinal plants using bioassay-based step-by-step purifications.

1. Antiplatelet agents

Platelets play important roles in physiological hemostasis and pathological thrombosis. Measurement of platelet function is an easy and simple procedure for the evaluation of biologically active components from herbal plant sources. We challenged platelet-rich plasma or washed platelets with various agonists, and monitored platelet aggregation and release of reaction products (ATP or serotonin). According to the mechanisms of action of the components on platelet aggregation, release of reaction products and signal transductions involved, these antiplatelet agents can be classified into eight groups: 1. platelet-activating factor (PAF) antagonists, 2. collagen-receptor antagonists, 3. thromboxane-receptor antagonists, 4. ADP-receptor agonists, 5. inhibitors of phosphoinositide breakdown, 6. inhibitors of thromboxane formation, 7. cyclic nucleotides increasing agents, and 8. protein kinase C activators. (Fig. 1) These novel pharmacological agents derived from medicinal plant sources may be useful as valuable leads for the development of effective antithrombotic drugs.

2. Vasorelaxants

For the evaluation of the fractions or purified components isolated from herbal plants, rat thoracic aortic strips were contracted by phenylephrine or in high potassium medium. According to their modes of action, these

vasorelaxing or anti-contractile agents can be classified into five groups: 1) α-adrenergic receptor antagonists, 2) thromboxane A_2 –receptor antagonists, 3) endothelium-derived relaxing factor (EDRF) releasing agent, 4) Ca^{2+}-channel blocking agents, and 5) Ca^{2+}-channel agonist which opens voltage-dependent channel (VOC) (Fig. 2).

3. Bronchodilators

By using contraction of isolated guinea-pig trachea smooth muscle as a test model, we found that some herbal components can cause bronchodilatation. According to their modes of action, they are classified into six groups: 1) Ca^{2+}-channel blocking agents, 2) thromboxane A_2 -receptor antagonists, 3) PAF-receptor antagonists, 4) muscarinic-receptor antagonists, 5) β_2-adrenoceptor agonists, and 6) phosphodiesterase inhibitors. Among these bronchodilators, CIS-19 was found to inhibit antigen-induced microvascular leakage, PAF- and antigen-induced bronchoconstriction, eosinophil recruitment into the airways, superoxide generation in bronchoalveolar lavage, and bronchial hyper-reactivity of guinea pigs. These results indicate that CIS-19 is potent in inhibition of PAF-induced airway response and may have therapeutic potential as an anti-inflammatory drug.

4. Prostate tissue relaxants

Prostate tissue is quite similar to vascular smooth muscle. In response to sympathomimetic agents, α-adrenoceptor is activated and initiate tissue contraction. We obtain prostate tissues from patients of benign prostate hyperplasia (BPH) in surgery. Some α–adrenoceptor antagonists have also been evaluated for their subtype specificity in various tissues, such as vas deference (α_{1A}), spleen (α_{1B}) and blood vessels (α_{1D}). However, the relative potencies toward the different subtype α–receptors are less than ten.

5. Cardiotonic and antiarrhythmic agents

Prof. Su, MC, of our department, undertook the screening tests in the myocardium or heart tissue. In one case of collaborative study with a pharmaceutical company, we organized a teamwork project for the development of a new anti-arrhythmic agent, which was partially synthesized from an aboriginal plant in Taiwan. However, the potential candidate drug was abandoned after we completed the pre-clinical experiments due to its low bioavailability (PO) and short half-life in plasma. New derivatives of this novel anti-arrhythmic agent are still being developed continually by Prof. Su.

6. Anti-oxidants and free-radical scavengers

The aggregation of platelets induced by exogenous arachidonic acid has been shown to be inhibited by many plant components. Their antiplatelet actions are quite similar to those of aspirin by inhibiting thromboxane formation. Cyclooxygenase, but not TxA_2 synthase, is thought to be the site of action because both TxA_2 and PGD_2 formation are

decreased in platelets, and PGE_2 formation is inhibited after incubation of sheep vesicular gland microsomes with arachidonic acid. The natural anti-oxidants may have cytoprotective effects against cellular damage in various tissues under oxidative stress.

7. Anti-inflammatory agents

Many of the antiplatelet agents are also potent anti-inflammatory agents; especially those that inhibit cyclooxygenase or/and lipoxygenase. We found those agents can inhibit the degranulation and aggregation of inflammatory cells, especially neutrophils, mast cells, These natural compounds can be further developed for the treatment of inflammation or edema.

8. Anti-proliferating agents

For the search of active components from herbal plants, we evaluated their effects on cell proliferation and apoptosis in various primary cells or cell lines, such as endothelial cells, vascular smooth muscle cells, cancer cell lines (prostate, liver, lung, breast, leukocytes, etc.). These studies form the major foci in our future works in drug research and development.

In cases of promising pharmacological effects of these biologically active compounds demonstrated in vitro, further evaluations of their in vivo effects are performed to test the potentiality for drug development. Sometimes the in vivo effect cannot be obtained due to the low bioavailability, short half-life in plasma, high plasma-binding activity, and low therapeutic index etc. Different potencies of the same compound are found in different animal models. Furthermore, single purified component may be less potent than the crude extract due to the loss of the synergistic actions of adjunct components. However, these purified compounds (Table 1) can be useful leads to be optimized and further developed as new drugs.

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