• 計畫中文名稱	微生物轉換 Stevioside 衍生物及 Glucocorticoid/Androgen Response Elements 之生物活性評估		
• 計畫英文名稱	Microbial Transformations of Stevioside Derivatives and Biological Evaluation on the Glucocorticoid/Androgen Response Elements		
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• 研究人員	林淑娟		
• 中文關鍵字	微生物轉換；甜菊醣；生物活性評估		
• 英文關鍵字	microbial transformation；stevioside；biological evaluation		
• 中文摘要	Glucocorticoid receptor (GR)以及 androgen receptor (AR)皆屬於 nuclear receptor superfamily，此兩種類固醇激素感受器於人體一些基本生理方面扮演關鍵性的角色。Glucocorticoids (GCs)及 androgens 皆透過細胞內的 GR 與 AR 以發揮其生理功能。GR 在結合到 cognate ligand 後，會專一性佔據 genomic glucocorticoid response elements (GRE)以達到其抗發炎作用；而活化的 AR 至細胞核與 DNA 上的 androgen response elements (ARE)結合後，導致基因轉錄的改變，以影響生長發展及調節男性生殖功能。合成的類固醇化合物，例如 dexamethasone 及 prednisolone，已被用於慢性發炎疾病的治療，但由於這些藥物也會同時抑制其它 steroid receptors，以致於產生副作用；steroidal androgens，主要爲 testosterone 及其衍生物，已被用於臨床上 androgen deficiency 的治療，然而廣泛利用雄性激素(androgens)來治療骨質疏鬆，則會受限於一些由 AR 所調控的副作用，因此研發具降低副作用產生之屬於 GC 或 androgen agonists 爲目前積極尋找的目標。微生物轉換具有位置及立體選擇性，因此可爲構造修飾有機化合物的一種工具。Stevioside 結構屬於四環二　的 ent-kaurene，具有多種生物活性。一般 bridged ring polycyclic diterpenoids 爲微生物轉換常用的受質，De Oliveira 等指出經由增加兩個或多個極性官能基的相加作用，也許可提高化合物既存的活性或產生新的生物活性，然而引入極性官能基，例如 OH group 於 unfunctionalised carbocyclic 結構是相當困難的，所以微生物轉換技術已被用爲化學反應的一種替換方法。由於 stevioside 本身具多樣性活性，加上構造特徵及來源易得，因此由其化學構造修飾後所得到屬於 ent-kaurane、ent-kaurene 或 ent-beyerane 骨架的四環二　類可作爲藥物研發的好的模板分子。爲了延伸此類化合物之化學及研究微生物酵素的反應性，未來三年將利用由 stevioside 化學衍生的四環二　化合物爲受質，		

	進行微生物轉換。由於四環二　類具有與類固醇類似的骨架，因此各年度所分離的轉換產物將對 GRE-及 ARE-mediated reporter gene 進行生物活性評估，以得到 potential GC 或 androgen agonists，建立一系列構造、活性之間的關係，此外也將對潛在有效化合物進行作用機轉與其它藥理及毒理方面之研究。
• 英文摘要	The glucocorticoid (GC) receptor (GR) and androgen receptor (AR) are members of the nuclear receptor superfamily of ligand-regulated transcription factors. These two steroid hormone receptors play pivotal roles in some of the most fundamental aspects of human physiology. Upon binding to cognate ligand, GR occupies specific genomic glucocorticoid response element (GRE) and modules the transcription of nearby genes, resulting in anti-inflammatory effects. After binding to the ligand, the activated AR may be translocated to the nucleus and bind to androgen response elements (AREs) on the target gene that affect development, growth, and regulation of male reproductive functions. Synthetic GCs such as dexamethasone and prednisolone have long been used to treat chronic inflammatory disease and immunomodulation but have side effects due to inhibition of other steroid receptors. Steroidal androgens, mainly testosterone and its derivatives, have been used clinically as replacement therapy for androgen deficiency. However, the broader use of steroidal androgens for additional treatments, such as osteoporosis, is limited by undesirable AR-mediated side effects. Thus, the development of GC agonists that exhibit a reduced incidence or reduced severity of side effects while maintaining potent anti-inflammatory activity, and androgen agonists with full anabolic activity but reduced impacts of undesirable effects and with an important role on endocrine therapies to treat muscle wasting and osteoporosis is currently a demanding goal. Microbial transformation is an important tool in the structural modification of organic compounds due to its significant regio- and stereo-selectivities. Stevioside, an ent-kaurene tetracyclic diterpenoid, possesses diverse biological activities. Bridged ring polycyclic diterpenoids are one class of studied substrates in microbial transformation. De Oliveira et al. indicated that it could be introduced the polar functionalities into unfunctionalized carbocycles or at chemically inactive positions, in order to enhance existing properties or lead to new biological activities. Thus, tetracyclic diterpenoids derived from stevioside could be as good prototype for drug development due to parent activities, structural features, and relative abundant. In an effort to produce new functionalized analogs with new biological activities, microbial transformation of stevioside derivatives will be undertaken in the next three years. Due to tetracyclic diterpenoids possessing a formal similarity to steroids, the transformation products will be evaluated on the GRE- and ARE-mediated luciferase reporter gene assay to obtain the potential GC and/or androgen agonists and establish structure-activity relationship. The results will provide a technical basis for further studying advances in action mechanism and associated pharmacological and toxicological effects.