藥用大麻中之大麻二酚
Cannabidiol in Medical Marijuana

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- 大麻 (Cannabis)簡介
- 大麻二酚 (CBD; cannabidiol) 治療人類疾病的作用機轉
- 大麻二酚 (CBD; cannabidiol) 治療癲癇的可能作用機轉
- 大麻二酚 (CBD; cannabidiol) 的製造、合成、代謝及藥物動力學特點
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大麻 (Cannabis)簡介
Introduction of cannabis

大麻相關名詞 (Terms related to cannabis)

Terms	
• 大麻 (Cannabis)	• 開花植物屬，包含熟知的熱帶大麻及印度大麻 ，西元前2700年已被中國神農氏用於醫療 (A genus of flowering plant with several recognized species such as sativa and indica. This plant is widely distributed and perhaps one of the oldest plants cultivated for human use. Its use had been described in Chinese pharmacopeias even around BCE 2700 for a number of medicinal indications by Emperor Shen Nung)
• 大麻 (Marijuana)	• 乾燥的大麻葉及花 (A dried mixture of cannabis leaves and flowers)
• 藥用大麻 (Medical marijuana)	• 醫療用的大麻或大麻製品 (Use of cannabis or cannabis product for medical purpose)
• 麻 (Hemp)	• 熱帶大麻莖幹中豐富的纖維，含微量四氫大麻酚及少量大麻二酚 (The hearty fibers in the stalk and stems of the plant Cannabis sativa L. It contains minimal amounts of THC and low levels of CBD)
• 麻油 (Hemp oil)	• 麻植物種子取得，內含可忽略的大麻素 (Obtained from the seeds of the hemp plant and contains a negligible amount of cannabinoids)
• 大麻二酚油 (CBD oil)	• 麻植物的花取得，不含四氫大麻酚 (Obtained from the flowering portion of the hemp plant and does not contain THC)
• 大麻油 (Cannabis oil)	• 濃縮的大麻萃取物，可能含高濃度四氫大麻酚 (It contains concentrated cannabis extract and may have a high THC concentration)
• 大麻素 (Cannabinoids)	• 與大麻素接受器交替作用的分子，包括 1) 超過100種自然產生的化學物質或植物性大麻素，包含四氫大麻酚及少量大麻二酚，2) 內源性大麻素在體內製造且與大麻素接受器結合，3) 合成大麻素在實驗室製造，與植物性大麻素或內生大麻素類似 (Molecules that interact with cannabinoid receptors. There are over 100 naturally occurring chemicals or phytocannabinoids including THC and CBD. Endocannabinoids are produced in the body and target the receptors. Synthetic cannabinoids are produced in the laboratory and mimic the phyto- or endocannabinoids)

Samanta D. Pediatr Neurol 2019; 96: 24-29

熱帶大麻 vs 印度大麻
Cannabis Sativa vs *Cannabis Indica*

熱帶大麻 vs 印度大麻
Cannabis Sativa vs *Cannabis Indica*

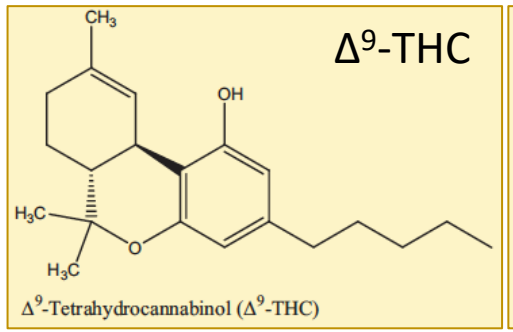
	Cannabis Sativa
• Origin	• Equatorial climates such as Thailand, southern Africa, and Mexico
• Cultivation	• 60-90 days to flower, good for outdoor grows in warm climates
• Plant features	• Tall, slim plants • Long, thin, light green leaves
• Bud features	• Lighter weight with subtle fruity aromas, sometimes hints of red and orange
• Treats	• Creative blocks, lack of focus, depression, fatigue
• Popular Stains	Sour Diesel, Green Crack, Amnesia Haze

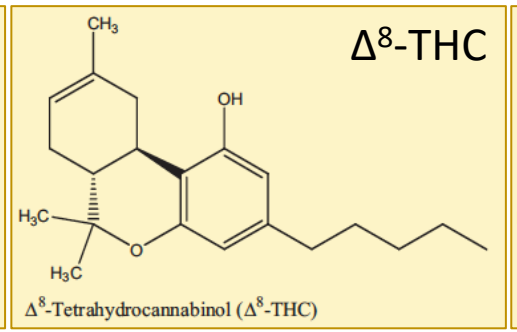
	Cannabis Indica
• Origin	• Mostly central Asia and the Indian subcontinent
• Cultivation	• 45-60 days to flower, higher yields, good for indoor grows
• Plant features	• Short, sturdy, and bushy plants • Short, wide, dark green leaves
• Bud features	• Dense with pungent aromas, sometimes purple
• Treats	• Insomnia, chronic pain, anxiety, loss of appetite
• Popular Stains	Purple Kush, Granddaddy Purple, Northern Lights

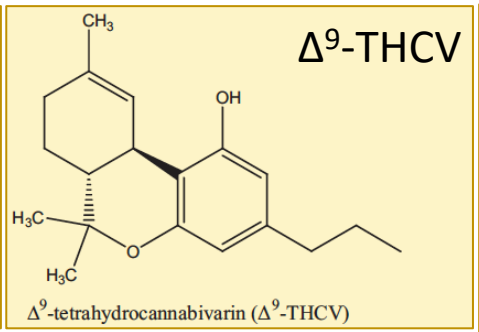
熱帶大麻 vs 印度大麻
Cannabis Sativa vs *Cannabis Indica*

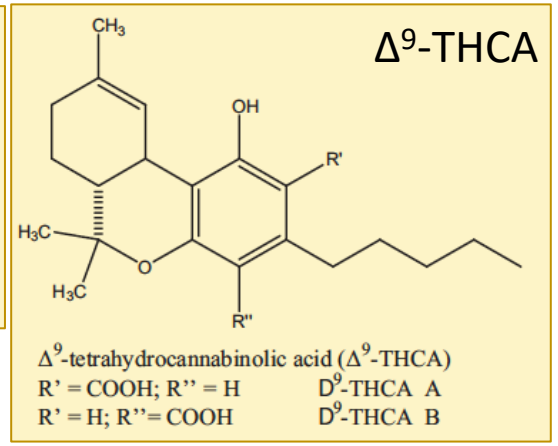
Cannabis Sativa	***Cannabis Indica***
• 中樞神經系統 high (Head high)	• 身體 high (Body high)
• 刺激 (Stimulating)	• 放鬆 (Relaxing)
• 白天使用 (Daytime use)	• 夜間使用 (Nighttime use)
• 警覺 (Alertness)	• 可做為鎮靜劑 (Acts as a sedative)
• 振奮及欣快感 (Uplifting and euphoria)	• 緩解疼痛 (Relives pain)
• 創造力 (Creativity)	• 刺激食慾 (Stimulates appetite)
• 緩解憂鬱 (Ease depression)	• 幫助睡眠 (Sleep aid)
• 促進活力 (Boosts energy)	
• 高CBD含量 (High CBD level)	• 高THC含量 (High THC level)

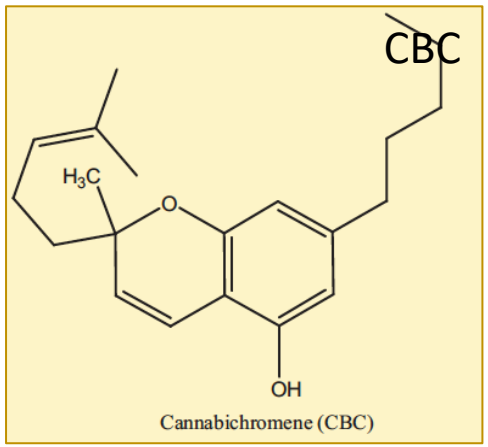
主要植物性大麻素的化學結構
Chemical structure of the main phytocannabinoids

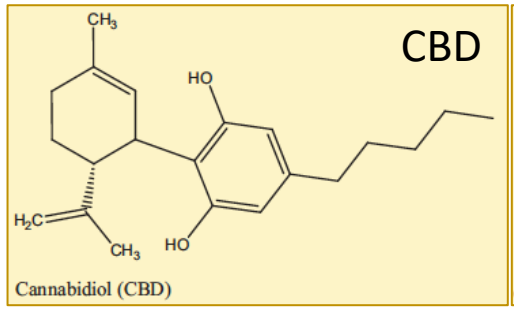


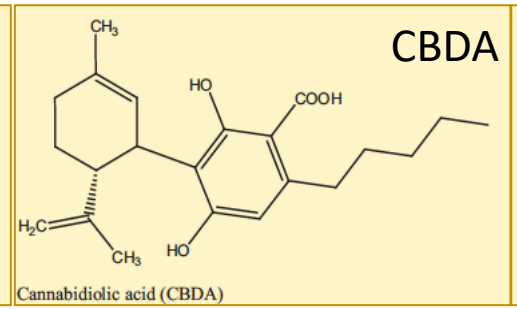


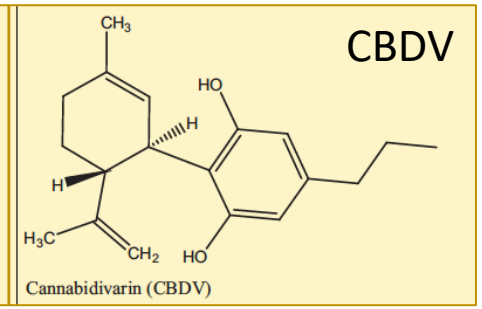


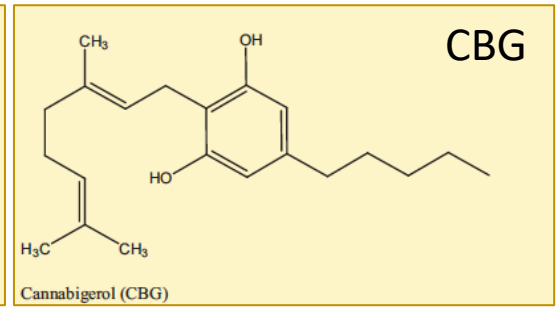


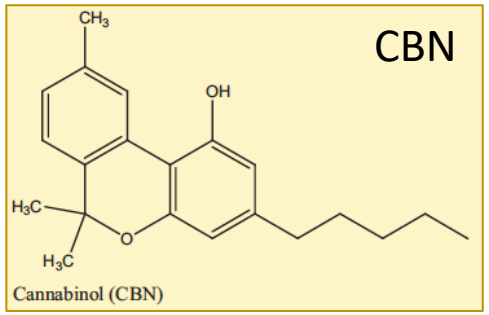






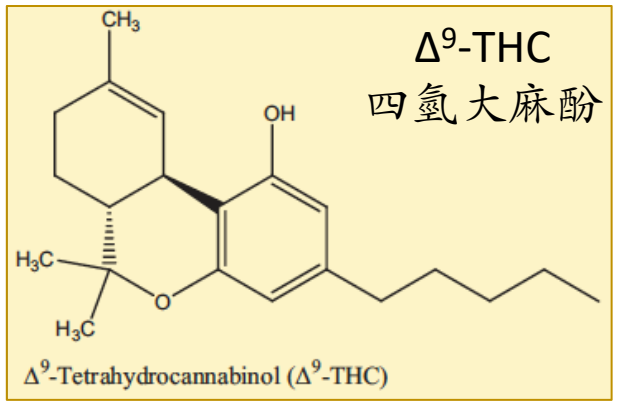


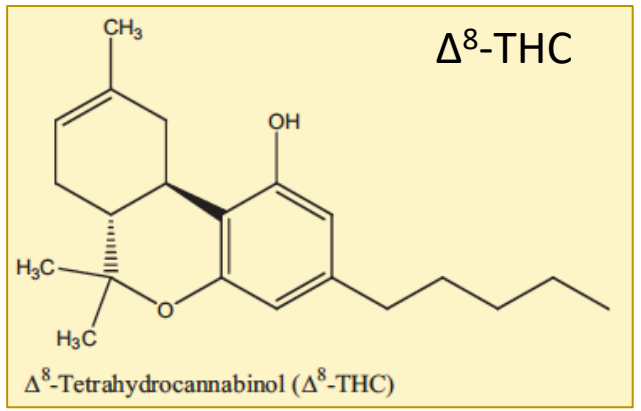


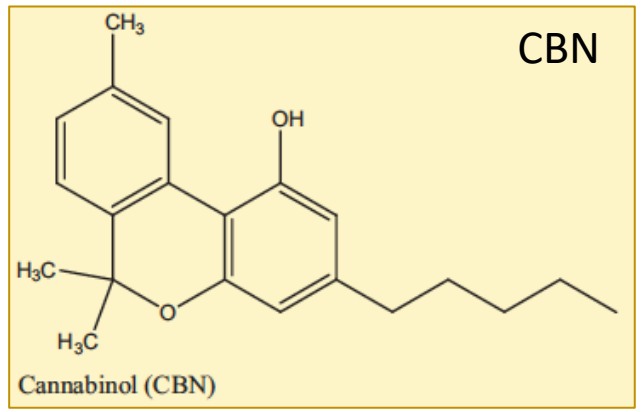


Izzo AA et al. Trends Pharmacol Sci 2009;30:515-527; Pisanti S et al. Pharmacol Ther 2017;175:133-150

主要植物性大麻素的化學結構
– 精神植物大麻素 -
Chemical structure and key information of the main phytocannabinoids
- Psychotropic (intoxicating) plant cannabinoids -







• Δ^9-THC (Δ^9-Tetrahydrocannabinol)	• Δ^8-THC (Δ^8-Tetrahydrocannabinol)	• CBN (Cannabinol)
• Primary psychotropic ingredient of *Cannabis* • Most abundant in drug-type plants • Partial agonist at CB1 & CB2 receptors • Activates TRPA1 & PPAR-γ	• An artefact resulted from isomerization of Δ^9-THC • Minuscule in *Cannabis*	• A product of Δ^9-THC oxidation • Weak CB1 agonist and CB2 partial agonist

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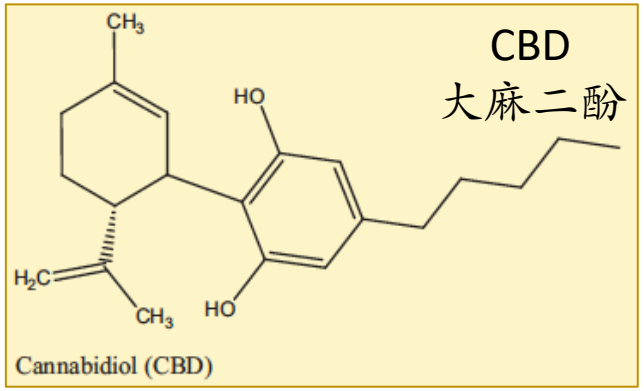
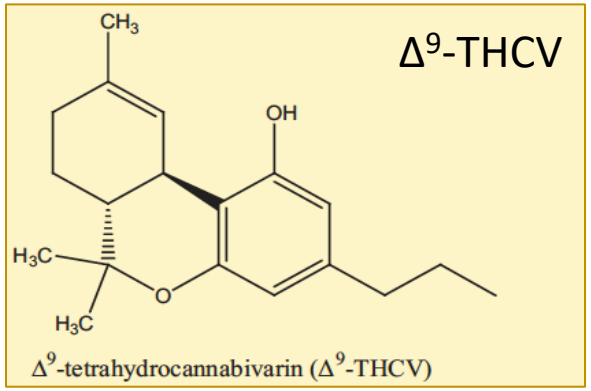
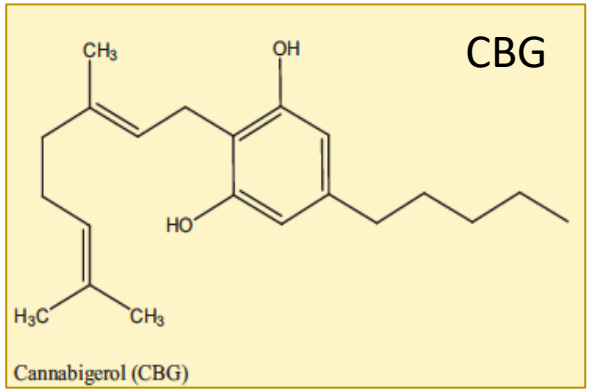
主要植物大麻素的化學結構
– 非精神(非中毒)植物大麻素 -
Chemical structure and key information of the main phytocannabinoids
- Non-Psychotropic (non-intoxicating) plant cannabinoids -







• CBD (Cannabidiol)	• Δ^9-THCV (Δ^9-Tetrahydrocannabivarin)	• CBG (Cannabigerol)
• A major non-psychotropic cannabinoid • Most abundant in fiber-type plants • Not specific antagonist of CB1 & CB2 • Inhibitor of AEA uptake metabolism	• Abundant in Pakistani hashish • Δ^9-THCV antagonizes Δ^9-THC at low dose (< 3mg/kg) • As a CB1 agonist at greater doses (10 mg/kg)	• A potent TRPM8 antagonist • TRPA1, TRPV1 and CB agonist • AEA reuptake inhibitor

AEA: anandamide

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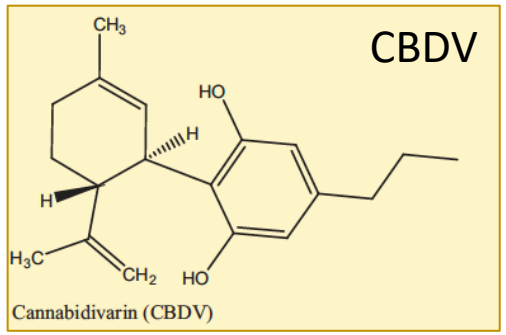

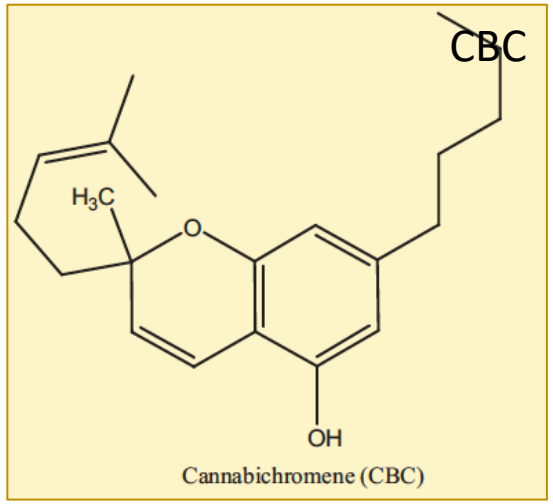

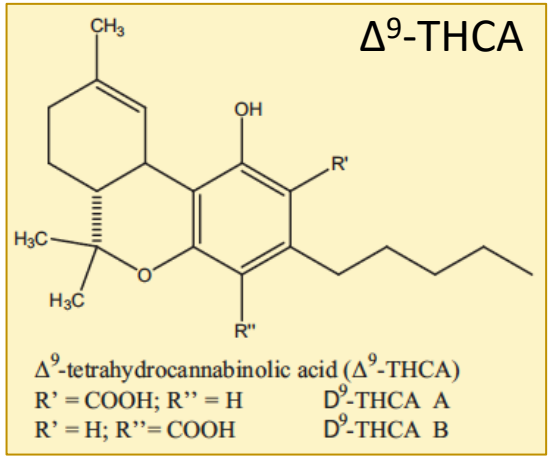

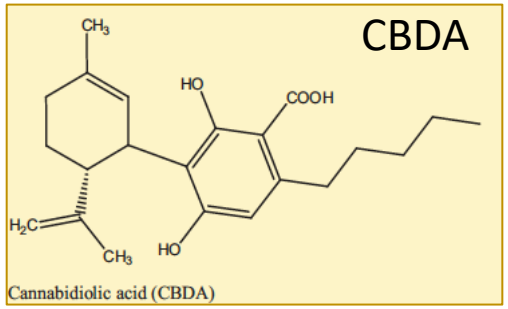

• CBDV (Cannabidivarin)	• CBC (Cannabichromene)	• Δ^9-THCA (Δ^9-Tetrahydrocannabinolic acid)	• CBDA (Cannabidolic acid)
• Unknown mechanism	• CBC with Δ^9-THC, the major cannabinoid in freshly harvested dry-type material • CBC is ~ 2.5 X more toxic than Δ^9-THC • Potential TRPA1 agonist • Inhibitor of AEA reuptake	• Δ^9-THC has 2 acidic analogs: Δ^9-THCA A and Δ^9-THCA B • Δ^9-THCA is a potent TRPA1 agonist and TRPM8 antagonist	• CBDA is the main component of glandular hairs (up to 15%) • Selective inhibitor of COX2 • TRPA1 and TRPV1 agonist • TRPM8 antagonist

AEA: anandamide

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非精神(非中毒)植物性大麻素的分子機轉

Proposed molecular mechanisms of the actions of non-psychotropic (non-intoxicating) phytocannabinoids

Phytocannabinoids	Mechanism	Pharmacological relevance
CBD	Antagonist of CB1/CB2 agonists	Antispasmodic effects
	CB2 inverse agonist	Anti-inflammatory effects
	FAAH inhibition	Reduce FAAH expression in the inflamed intestine
	Anandamide reuptake inhibitor	To be determined
	GPR55 antagonist	To be determined
	Positive allosteric modulator at α1 and α1β glycine receptor	Relief chronic pain after inflammation or nerve injury
	μ opioid receptor ligand	To be determined
	Positive allosteric modulator at μ and δ opioid receptors	The effects occurs at very high concentrations
	TRPA1 agonist	Analgesic effects
	TRPM8 antagonist	Analgesic effects
	TRPV1 agonist	Antipsychotic and analgesic effects
	TRPV2 agonist	The effect is shared by Δ^9-THC and CBN
	Adenosine uptake competitive inhibitor	Anti-inflammatory effects
	PPARγ agonist	Vasorelaxation and fibroblast stimulation
	5-HT1A agonist	Antischemic and anxiolytic properties
	Antagonist of the putative abnormal-CBD receptor	CBD attenuates the vasodilator response to anandamide
	Regulator of intracellular [Ca2+]	Neuroprotective and **antiepileptic** properties
	T-type Ca2+ channel inhibitor	Nociception and **antiepileptic** effects
	Suppression of tryptophan degradation	Role in pain, inflammation and depression
	5-Lipoxygenase inhibitor	CBD decreases 5-lipoxygenase in tumor tissues
	15-Lipoxygenase inhibitor	Anti-atherosclerosis
	Phospholipase Az modulator	Anti-inflammatory effects

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Proposed molecular mechanisms of the actions of non-psychotropic (non-intoxicating) phytocannabinoids

Phytocannabinoids	Mechanism	Pharmacological relevance
Δ^9-THCV	**CB1 antagonist**	Increases central inhibitory neurotransmission – with a therapeutic potential in **epilepsy**
	CB2 partial agonist	Stimulates mesenchymal stem cells
CBG	CB1 and CB2 partial agonist	To be determined
	Anandamide reuptake inhibitor	To be determined
	TRPA1 agonist	Analgesia
	TRPV1 agonist	Analgesia
	TRPM8 antagonist	Analgesia and treatment of prostate carcinoma
	Phospholipase A2 modulator	CBG reduces PGE2 release in human synovial cells
CBC	TRPA1 agonist	Analgesia
	Anandamide reuptake inhibitor	To be determined
Δ^9-THCA	TRPA1 partial agonist	Analgesia
	TRPM8 antagonist	Analgesia
CBDA	TRPA1 partial agonist	Analgesia
	TRPV1 agonist	Analgesia
	TRPM8 antagonist	Analgesia
	COX-2 inhibitor	To be determined

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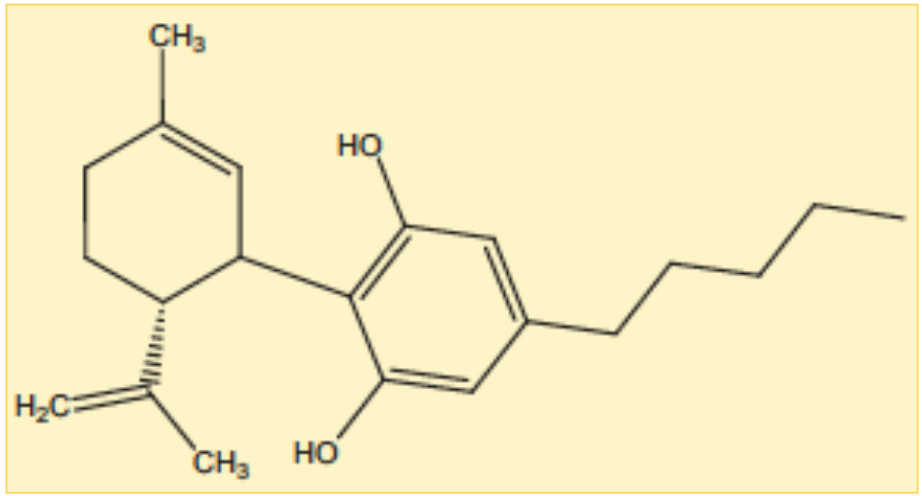
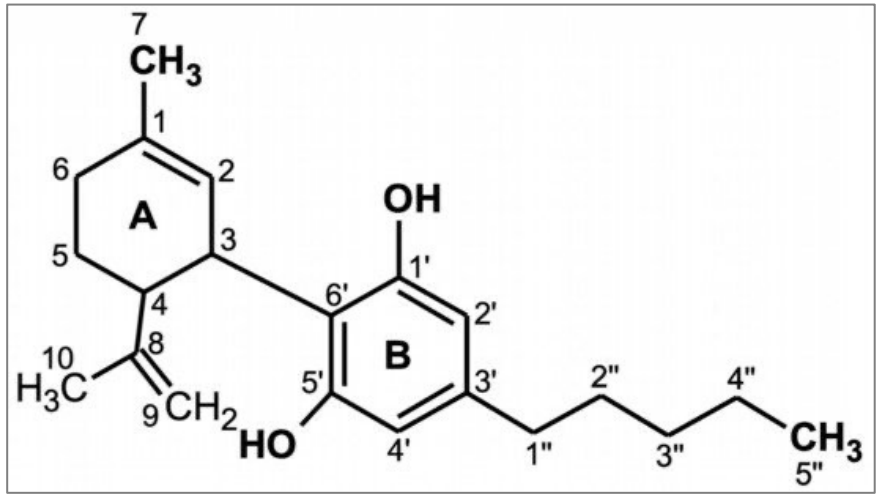
大麻二酚治療人類疾病的作用機轉
Mechanism of action of cannabidiol (CBD) for human diseases

大麻二酚 (CBD; cannabidiol)
Cannabidiol (CBD)

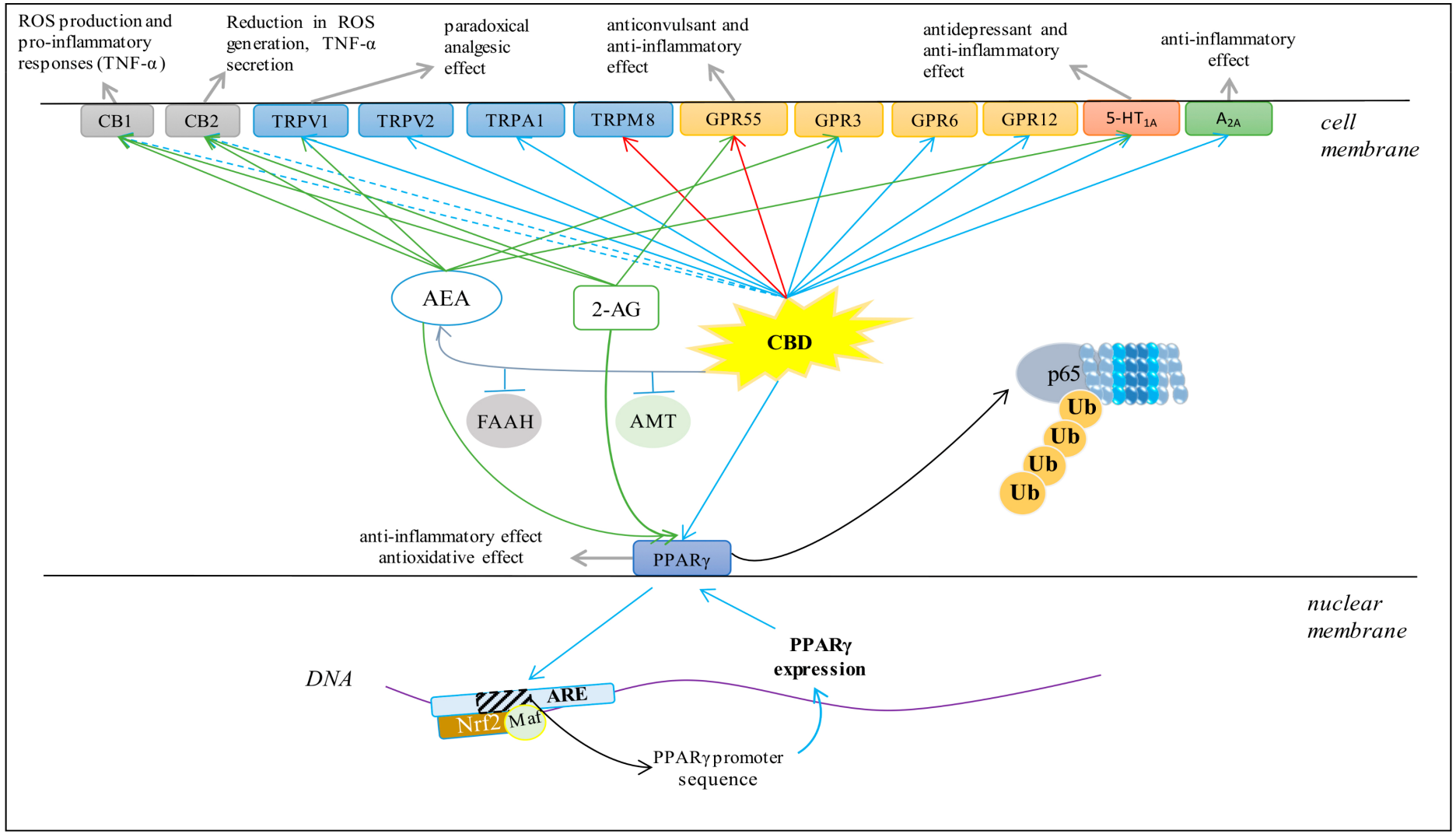
- A major non-psychotropic (non-intoxicating) cannabinoid
- 1940, first isolated by Adams and coworkers
- 1963, structure and stereochemistry determined by Mechoulam and Shvo





Izzo AA et al. Trends Pharmacol Sci 2009;30:515-527; Atalay S et al. Antioxidants 2020;9:21

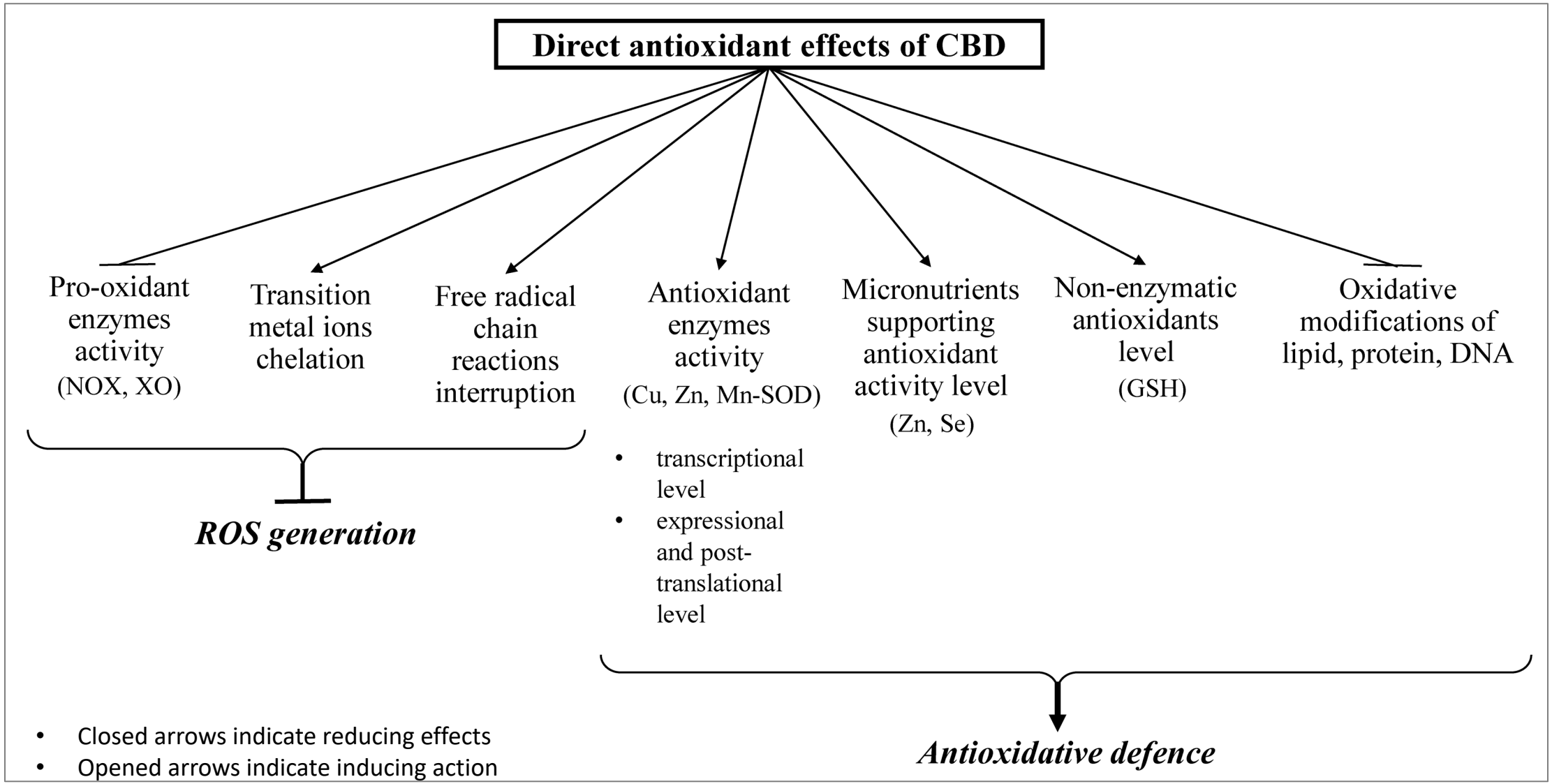
大麻二酚（CBD; cannabidiol）在細胞膜接受器上的主要作用
Major effects of CBD on several membrane receptors



- AEA, anandamide; 2-AG, 2-arachidonoylglycerol; FAAH, fatty acid amide hydrolase; AMT, AEA membrane transporter; ROS, reactive oxygen species; Ub, ubiquitin; p65, transcription factor NF-κB; Nrf2, nuclear factor erythroid 2-related factor 2; ARE, antioxidant response elements.
- Blue arrows indicate agonist activity; red arrows indicate antagonist activity; dashed blue arrows indicate weakly agonistic activity; green arrows indicate endocannabinoid agonist activity; grey arrows indicate chemical and biological effects

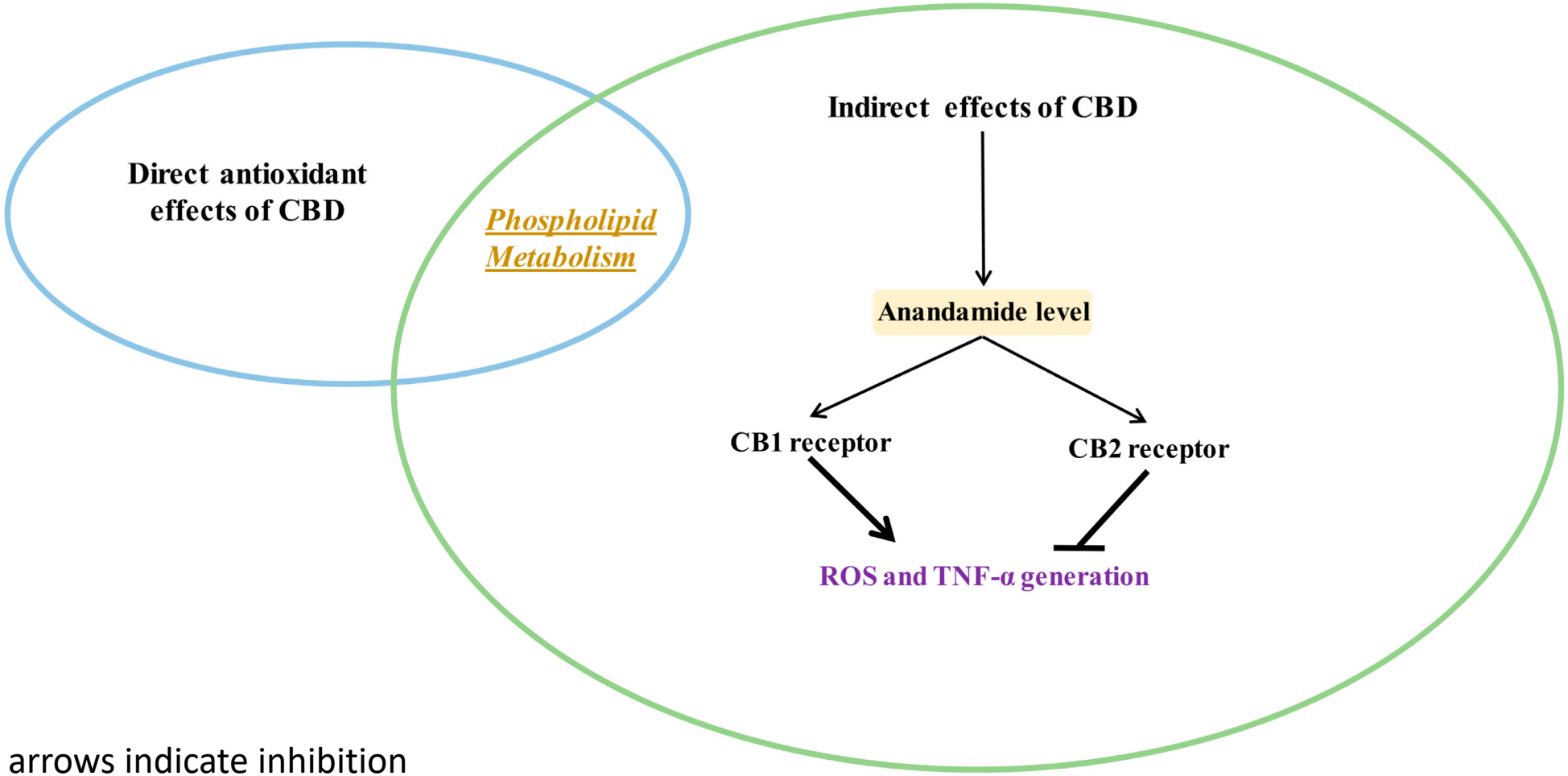
Atalay S et al. Antioxidants 2020;9:21

大麻二酚（CBD; cannabidiol）具直接抗氧化作用
Direct antioxidant effects of CBD



Atalay S et al. Antioxidants 2020;9:21

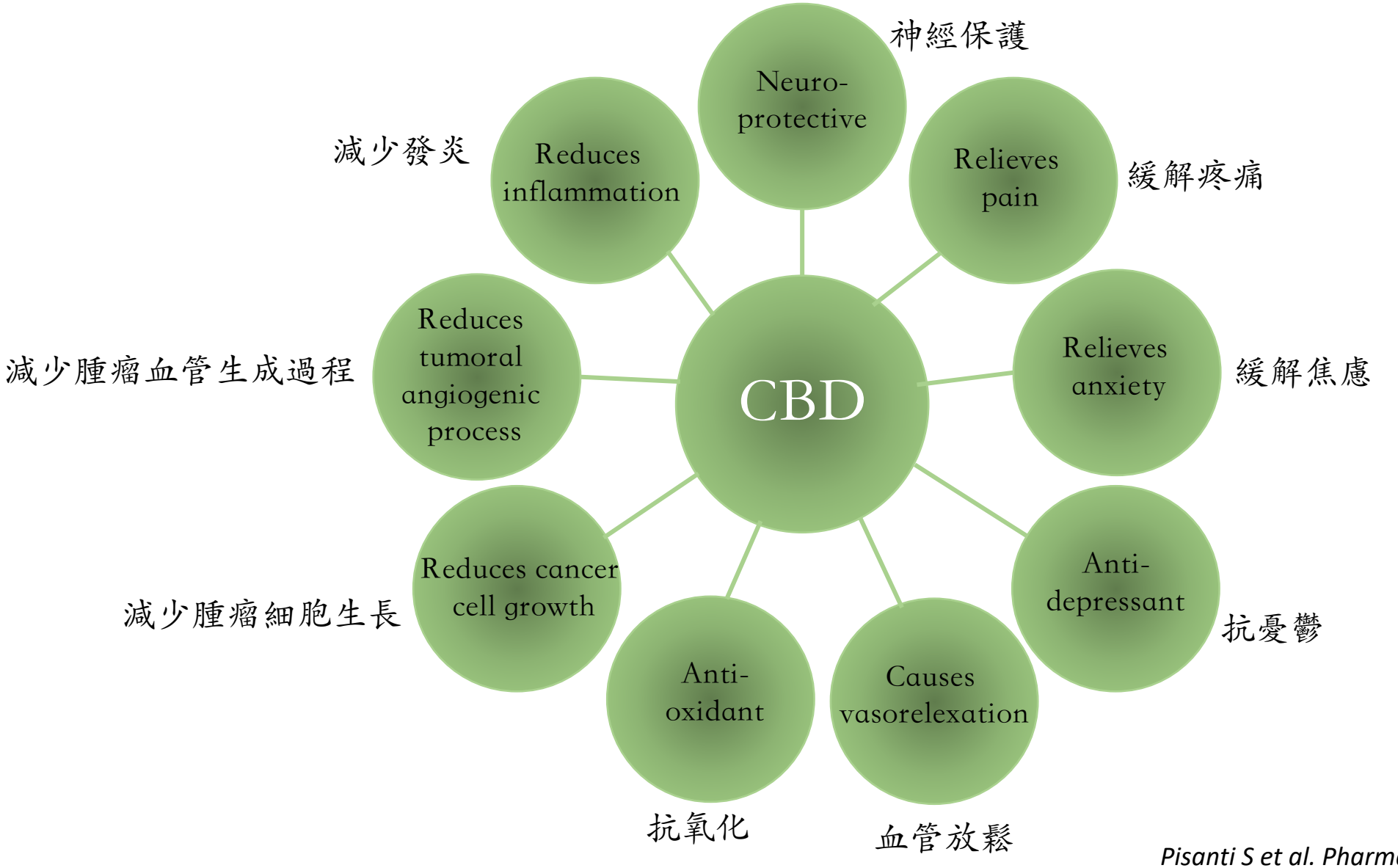
大麻二酚（CBD; cannabidiol）具間接抗氧化及抗發炎作用
Indirect antioxidant and anti-inflammatory effects of CBD



- Closed arrows indicate inhibition
- Opened arrows indicate activation

Atalay S et al. Antioxidants 2020;9:21

大麻二酚 (CBD; cannabidiol) 的多面向藥理作用
Multifaceted pharmacological effects of CBD



Pisanti S et al. Pharmacol Ther 2017;175:133-150

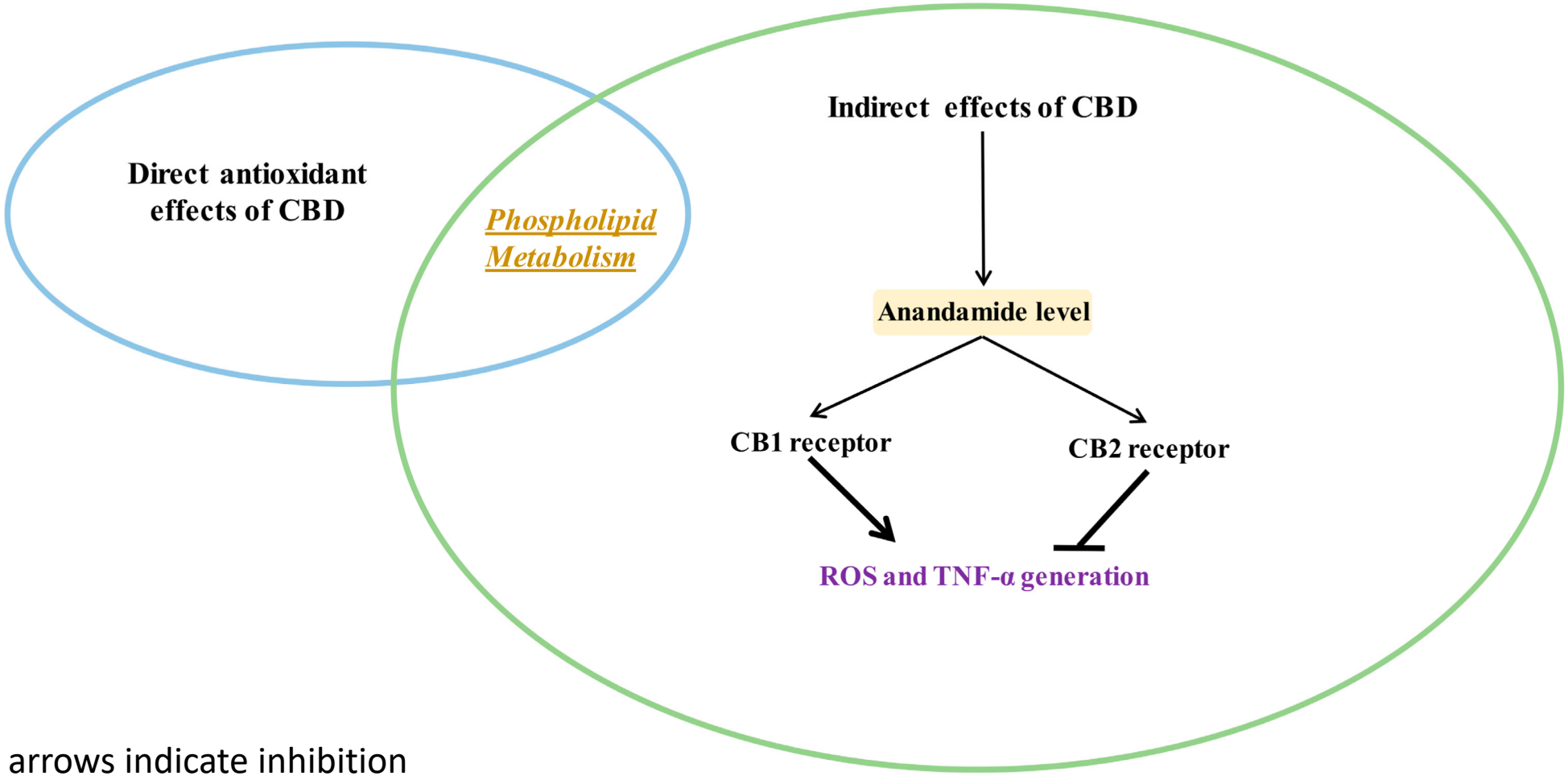
大麻二酚 (CBD; cannabidiol) 的藥理作用
CBD pharmacological effects

中樞神經系統 (CNS)	中樞神經系統以外 (Extra-CNS)
• 阿茲海默症 (Alzheimer's disease) • 帕金森氏症 (Parkinson's disease) • 多發性硬化症 (Multiple sclerosis) • 癲癇 (Epilepsy) • 亨丁頓舞蹈症 (Huntington's disease) • 缺血缺氧傷害 (Hypoxia-ischemic injury) • 疼痛 (Pain) • 焦慮 (Anxiety) • 憂鬱 (Depression)	• 腫瘤 (Cancer) • 噁心 (Nausea) • 發炎疾病 (Inflammatory diseases) • 風濕性關節炎 (Rheumatoid arthritis) • 感染 (Infection) • 發炎性腸症 (Inflammatory bowel and Chron's disease) • 心血管疾病 (Cardiovascular diseases) • 糖尿病併發症 (Diabetes complications)

Pisanti S et al. Pharmacol Ther 2017;175:133-150

大麻二酚 治療癲癇的可能作用機轉
Proposed mechanism of action of CBD in epilepsy

大麻二酚（CBD; cannabidiol）具間接抗氧化及抗發炎作用
Indirect antioxidant and anti-inflammatory effects of CBD



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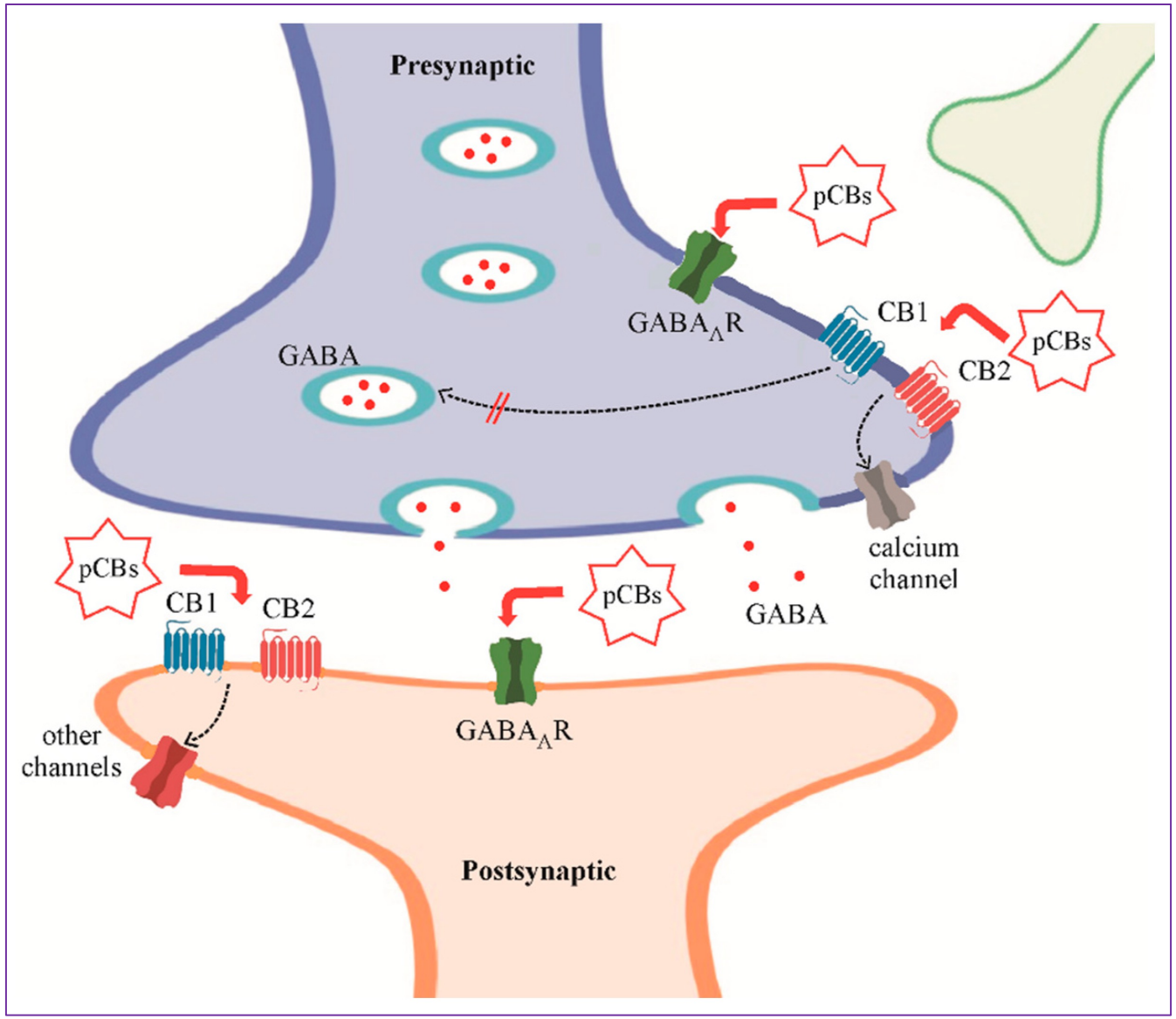
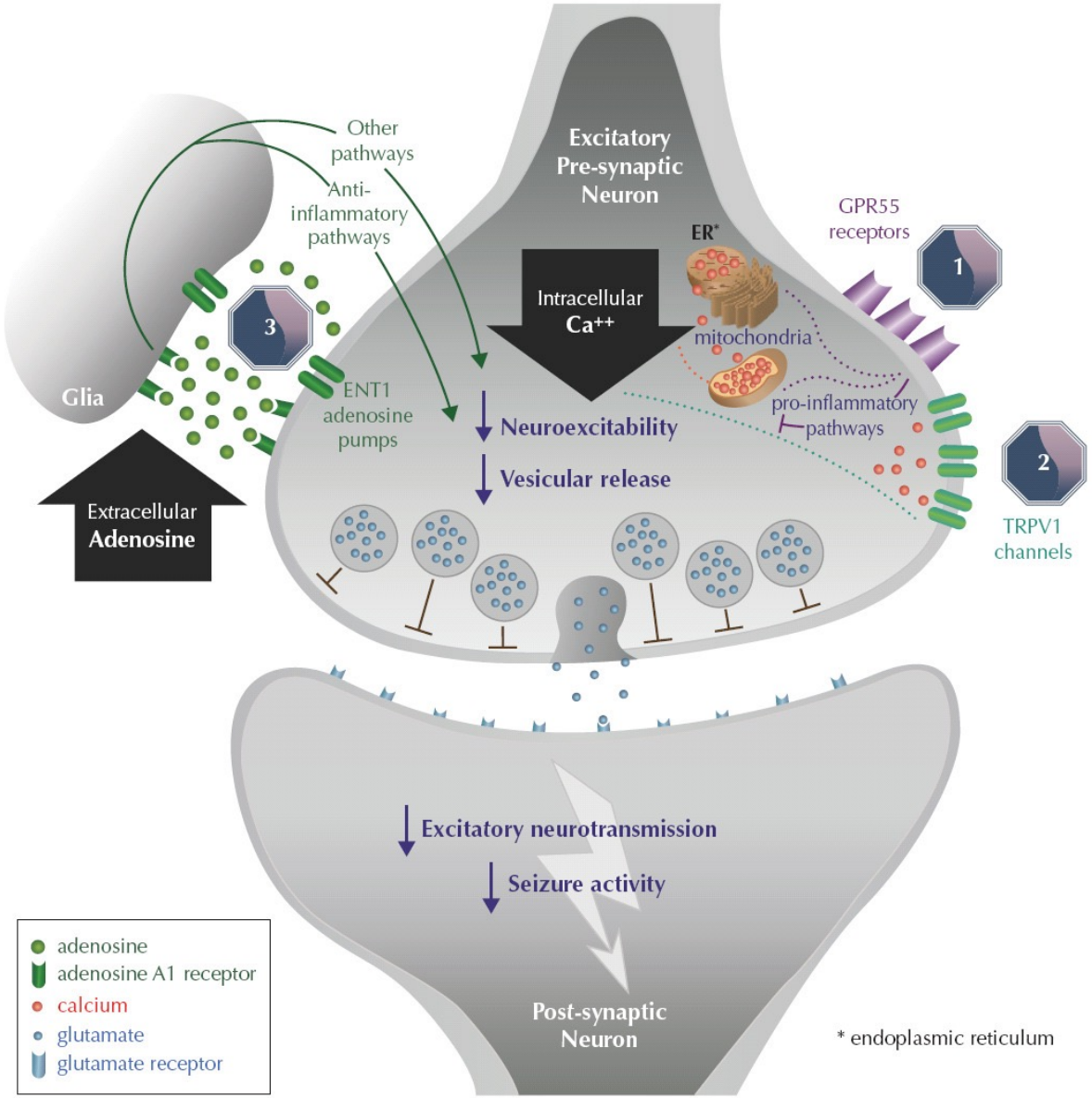
大麻素在神經疾病中會影響GABA
Cannabinoids on Neurological Diseases with GABA Involvement



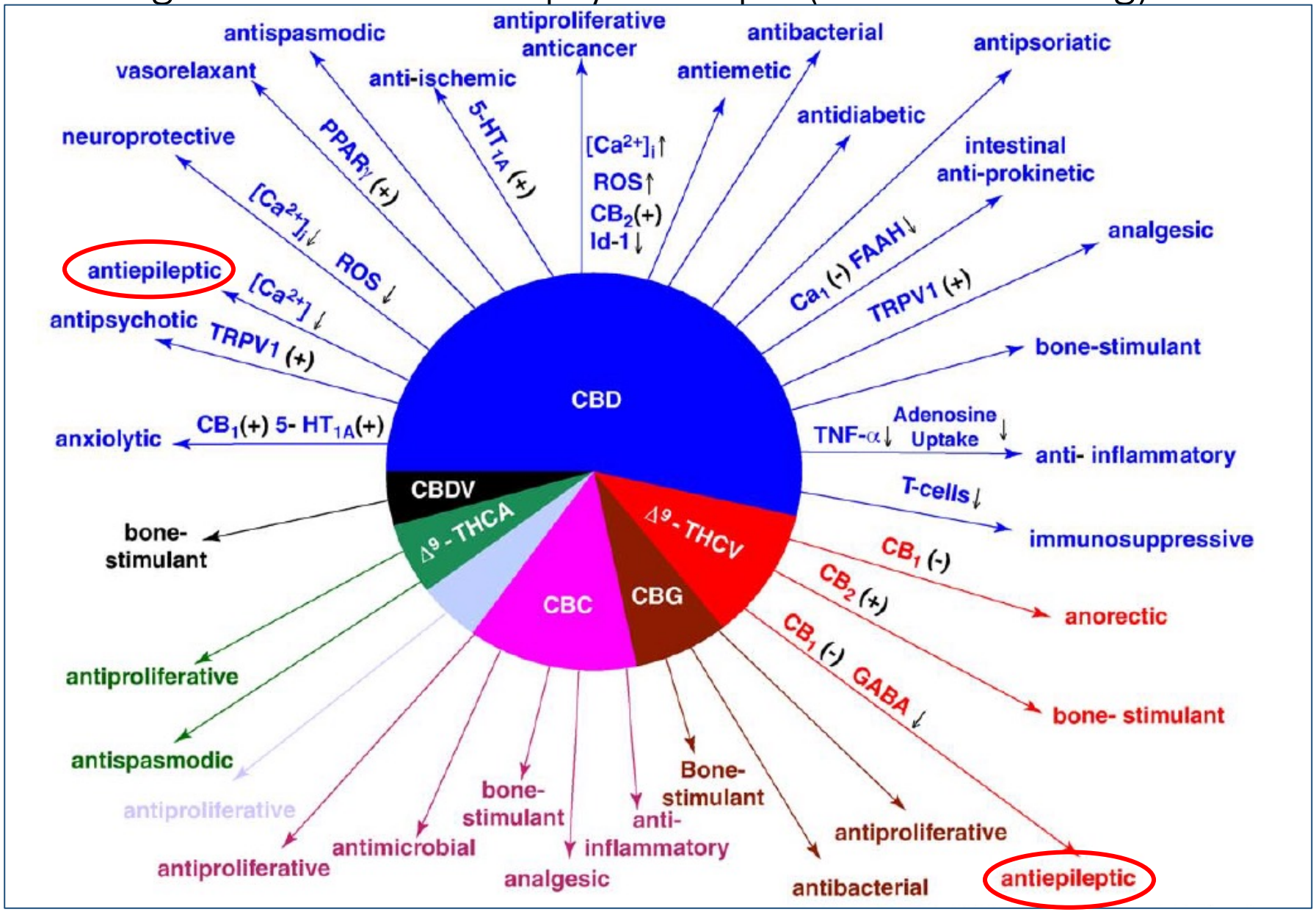
Cifelli P et al. Int J Mol Sci 2020;21:723

大麻二酚治療癲癇的多模式可能作用機轉
Proposed multimodal mechanism of action of CBD in epilepsy



Gray RA and Whalley BJ. Epileptic Disord 2020; 22 (Suppl 1): S10-S15

非精神(非中毒)大麻素的藥理作用
Pharmacological actions of non-psychotropic (non-intoxicating) cannabinoids

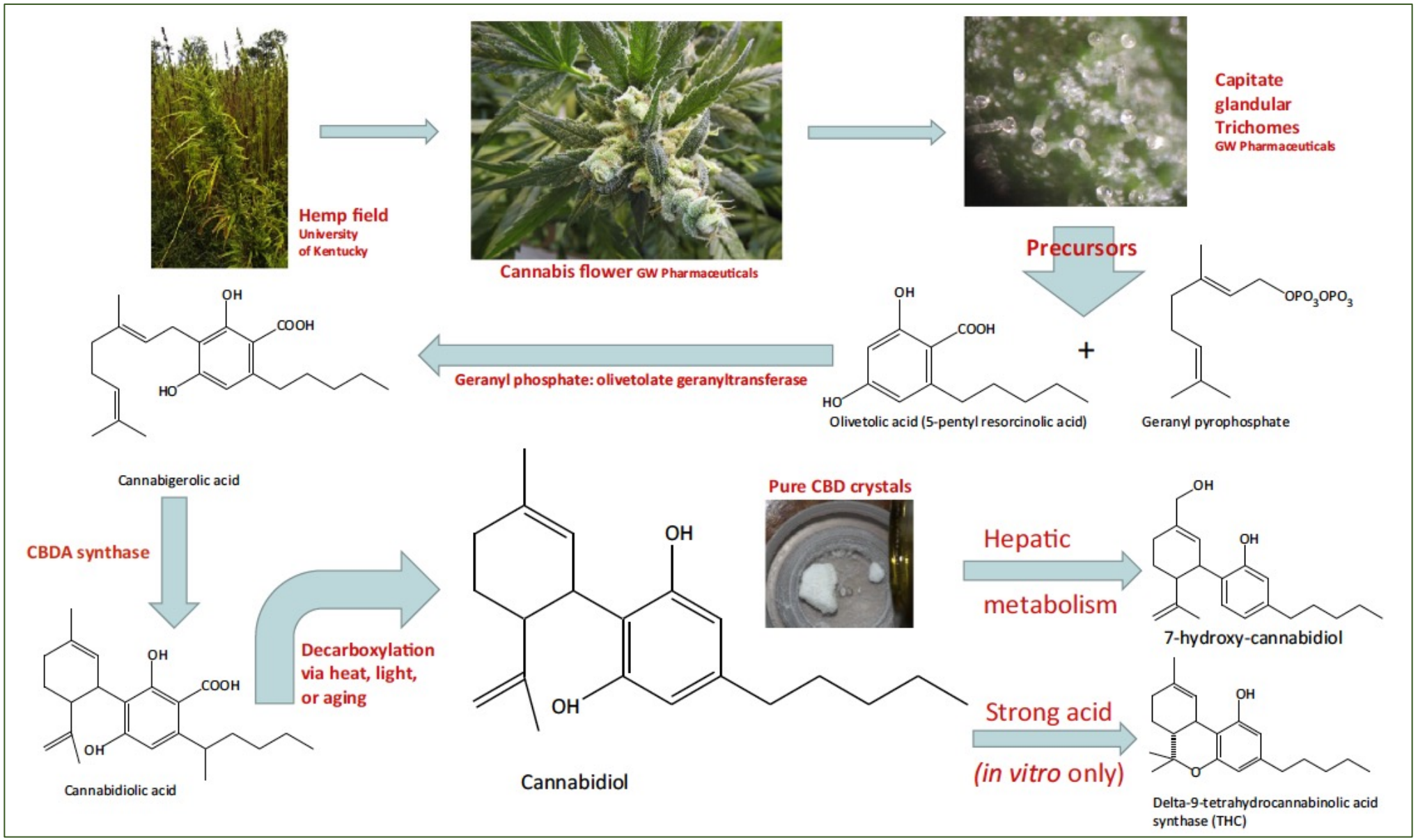


Izzo AA et al. Trends Pharmacol Sci 2009;30:515-527

大麻二酚 (CBD; cannabidiol) 的製造、合成、代謝及藥物動力學特點

CBD production, biosynthesis, metabolism, and pharmacokinetic characteristics

大麻二酚 (CBD; cannabidiol) 的製造、合成、代謝
CBD production, biosynthesis, and metabolism



Russo EB. Trends Pharmacol Sci 2017;38:198-201

大麻二酚 (CBD; cannabidiol) 的藥物動力學特點
Pharmacokinetic characteristics of CBD

	Pharmacokinetic properties	Comments
Absorption	• Bioavailability ~ 6% • T_{max} 90-120 min • Oral oil formulation	• Minimal absorption • Extensive first-pass metabolism through CYP3A4 • Substantial variability between patients, > 4-5-fold with a fat-rich meal
Distribution	• Protein binding 94-99% • Vd 20-40.000 L!	• Variability in free fraction? • Displacement in interactions ?
Metabolism	• CYP3A4, CYP2C19 • UGT1A7, UGT1A9, UGT2B7 • $t_{1/2}$ 24-60h	• Strong enzyme-inhibiting properties, PGP? Active metabolite, 7-OH-CBD
Excretion	• Faeces, urine • Unchanged 12%	

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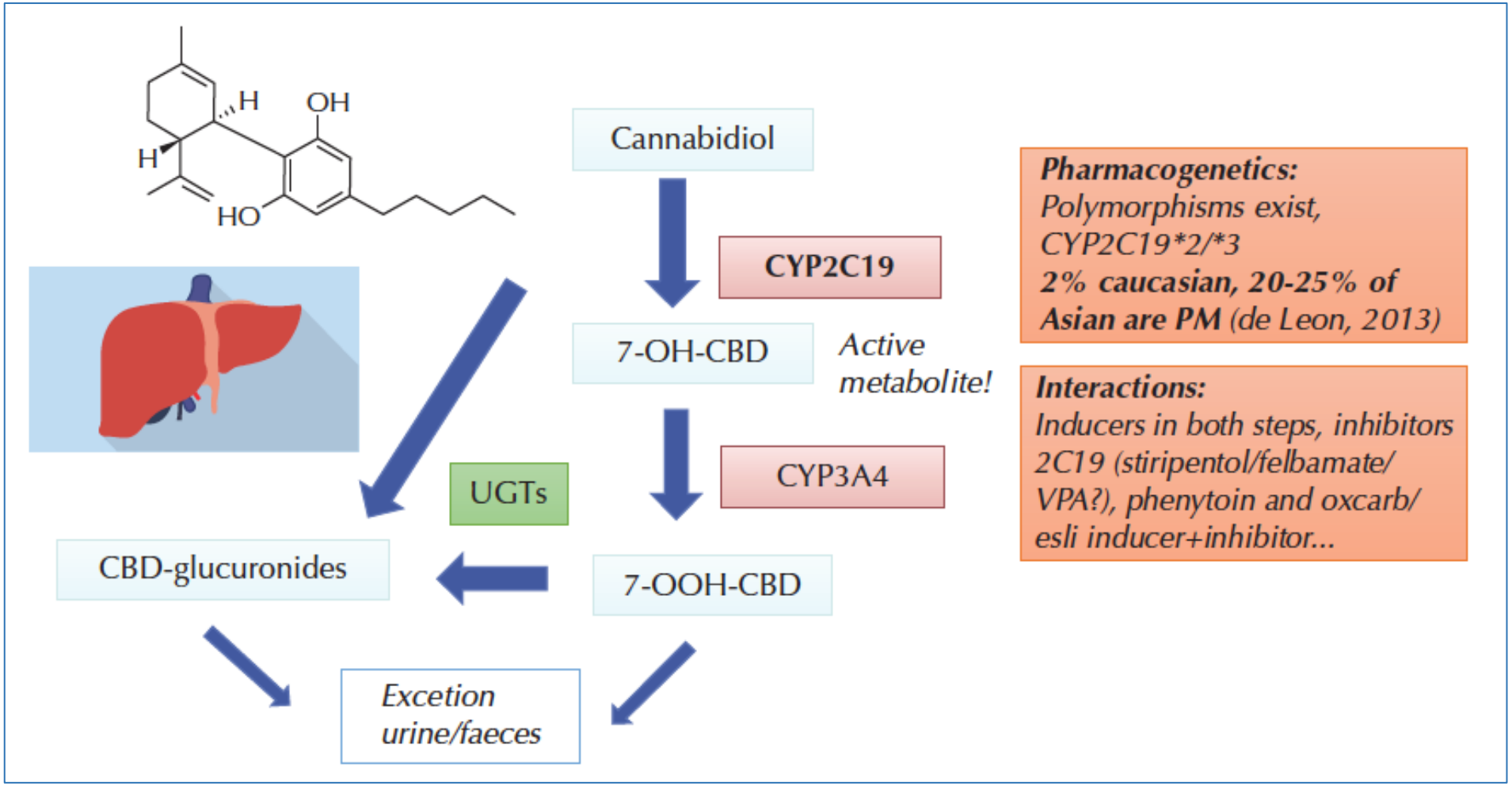
Drug interaction

- Additive (1+ 1 =2)
- Synergistic (1+ 1 > 2)
- Antagonistic (1 + 1 < 2)

大麻二酚（CBD; cannabidiol）的代謝
Metabolism of CBD



- 7-hydroxy-CBD (7-OH-CBD) is an active metabolite
- Carboxylic acid (7-OOH-CBD) is regarded as an inactive metabolite

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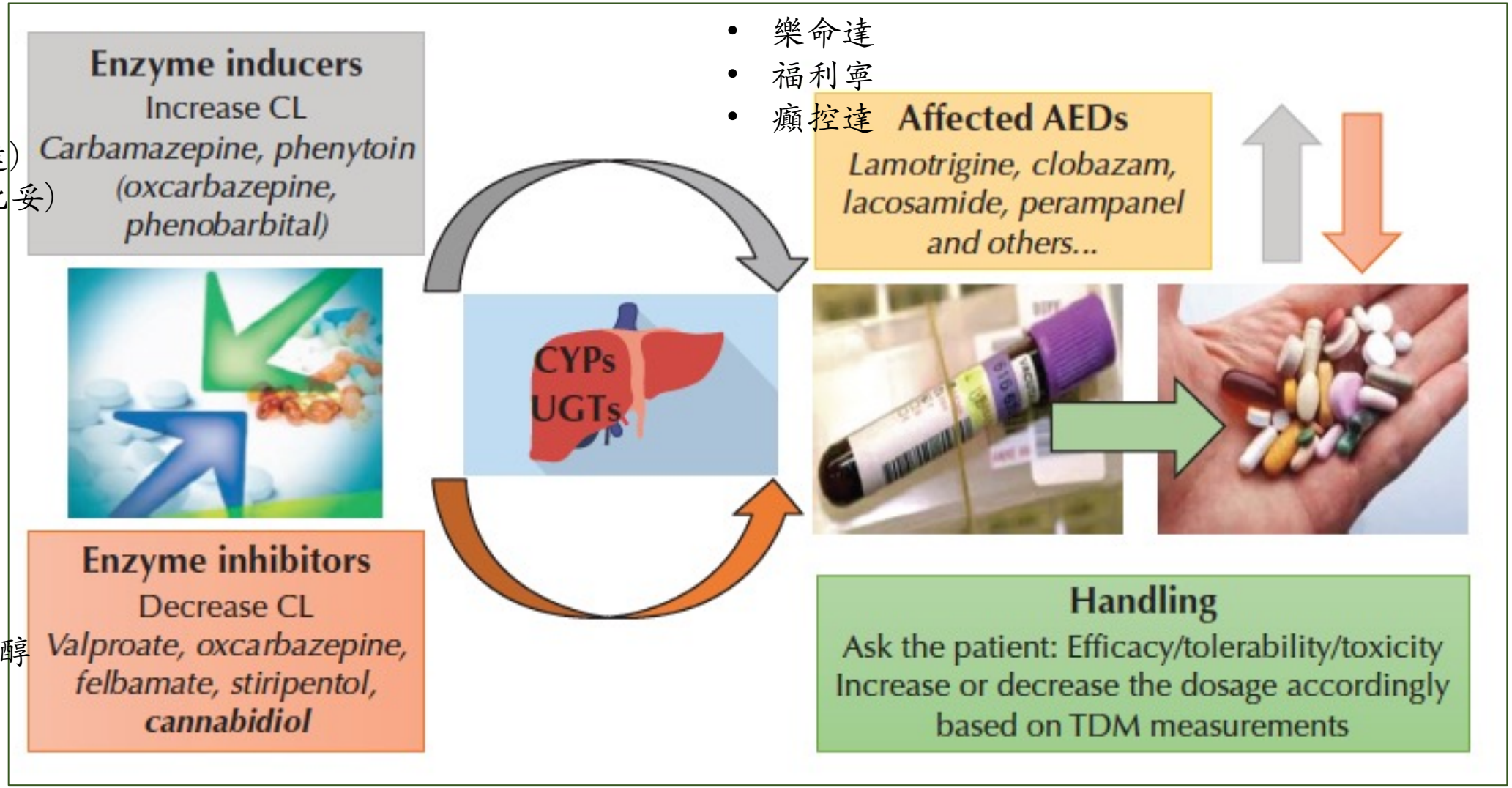
大麻二酚與抗癲癇藥物的藥物動力學交替作用
Pharmacokinetic interactions with AEDs

- 癲通
- 癲能停
- (除癲達)
- (苯巴比妥)

- 樂命達
- 福利寧
- 癲控達



- 帝拔癲
- 除癲達
- 司替戊醇

CL: clearance

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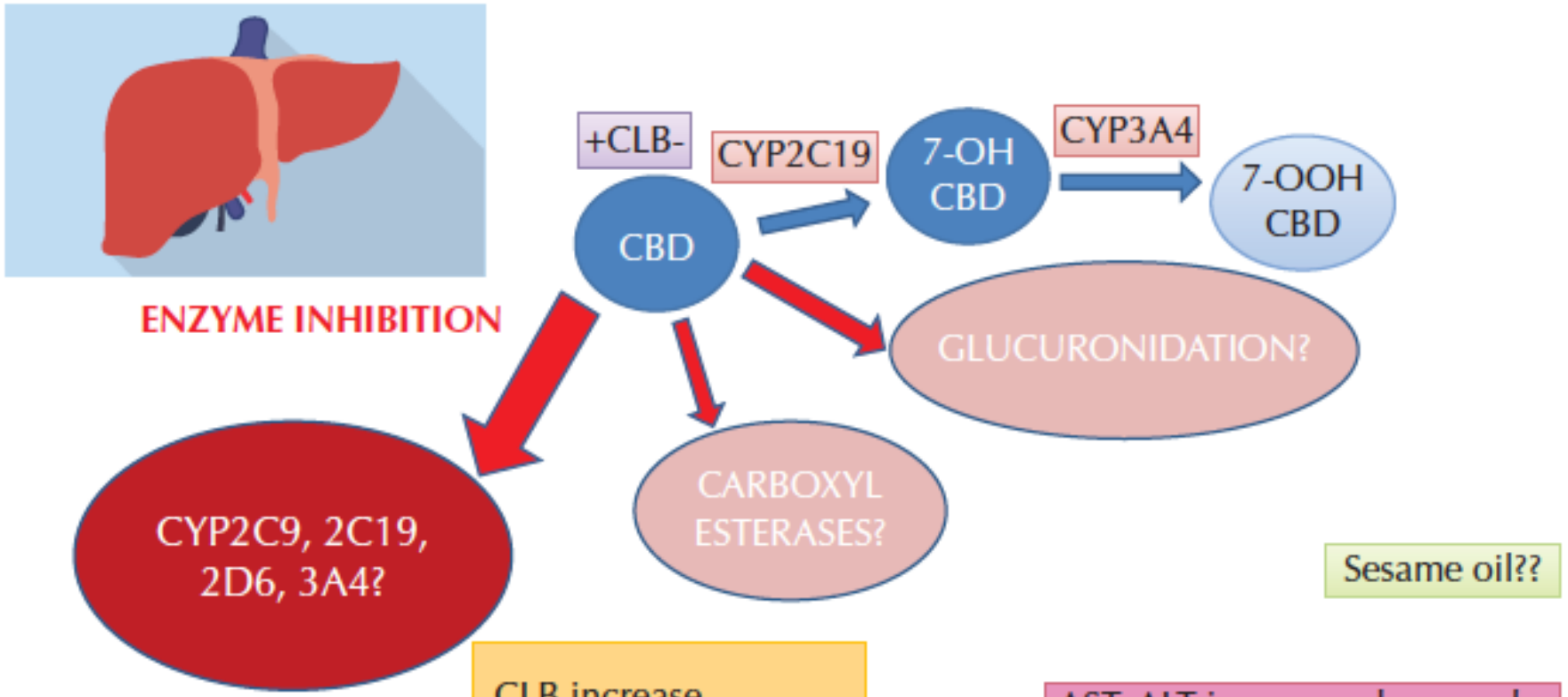
抗癲癇藥物與大麻二酚的藥物動力學交替作用
Pharmacokinetic interactions with CBD



- 大麻二酚加上福利寧會使福利寧活性代謝產物濃度上升5倍
- 大麻二酚加上帝拔癲可能會使肝功能上升

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藥物間的交替作用
Potential drug interactions

Enzyme	Substrates	Drug-drug interaction
• Moderate or strong inhibitor of CYP3A4 or CYP2C19	• Amiodarone, Erythromycin, Fluconazole, Verapamil (維帕特), etc	• These can increase CBD plasma concentration
• Strong CYP3A4 or CYP2C19 inducer	• Rifampicine	• These can decrease CBD plasma concentration
• Substrates of UGT1A9	• Diflunisal, Propofol, Fenofibrate	• CBD can inhibit the enzyme activity and increase the concentration of dosage of substrates
• Substrates of UGT2B7	• Gemfibrozil, Lamotrigine (樂命達), Morphine, Lorazepam	• CBD may inhibit the enzyme activity and increase the concentration of dosage of substrates
• Clobazam		• Level of the active metabolite of clobazam (N-desmethylclobazam) may increase by 5 fold, a potential for added benefit with an increased risk of side effects
• Substrates of CYP2C8	• Montelukast	• CBD may inhibit the enzyme activity and increase the concentration of the substrates
• Substrates of CYP2C9	• Phenytoin (癲能停)	• CBD may inhibit the enzyme and increase the concentration of the substrates
• Substrates of CYP1A2	• Theophylline, Caffeine	• CBD may induce or inhibit the enzyme activity, and increase or decrease of the dosage may be necessary
• Substrates of CYP2B6	• Bupropion, Efavirenz	• CBD may induce or inhibit the enzyme activity, and increase or decrease of the dosage may be necessary

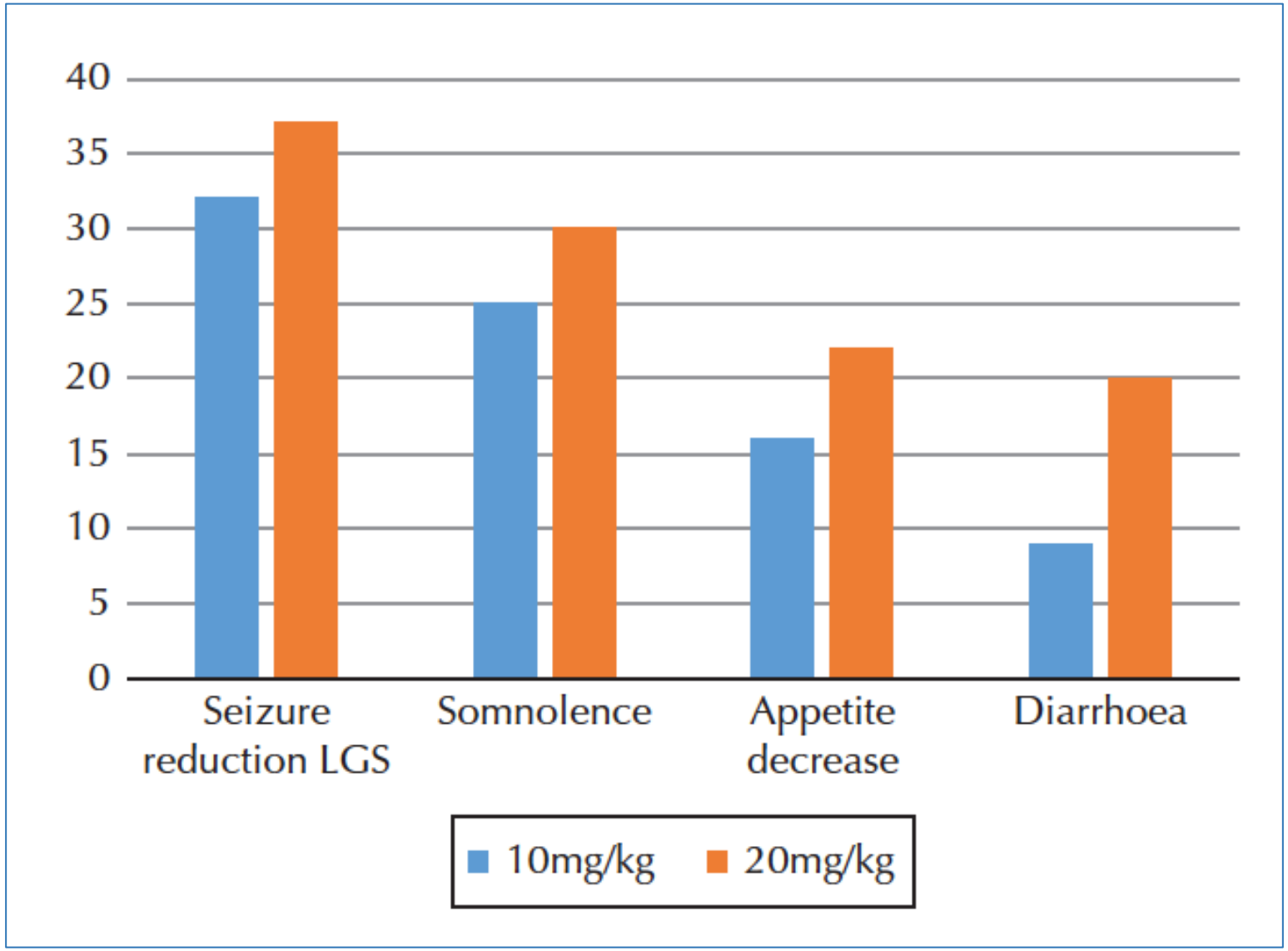
Samanta D. Pediatr Neurol 2019; 96: 24-29

大麻二酚與常用抗癲癇藥物間的交替作用
Interactions between cannabidiol and commonly used AED

CBD	AED
• 兒童及成人增加大麻二酚劑量 (↑ CBD dose in children and adults)	• 增加妥泰濃度；↑ [Topiramate] • 增加克雷格濃度; ↑ [Rufinamide] • 增加福利寧代謝產物濃度; ↑ [N-des-methylclobazam] • 降低福利寧濃度; ↓ [Clobazam]
• 成人增加大麻二酚劑量 (↑ CBD dose in adults)	• 增加左能安濃度; ↑ [Zonisamide] • 增加艾司利卡西平濃度; ↑ [Eslicarbazepine]
• 大麻二酚加上帝拔癲 (CBD + Valproate)	• 肝臟酵素上升 (Higher AST and ALT levels)

Gaston TE et al. Epilepsia 2017;58:1586-1592

大麻二酚劑量依賴的療效
Dose dependency of efficacy



Landmark CJ and Brandl U. Epileptic Disord 2020; 22(Suppl):S16-S22

市售藥用大麻二酚
CBD in the market

Cannabidiol (Epidiolex)

Cannabidiol (Epidiolex), Quick facts

- FDA適應症：用於大於或等於2歲的卓飛症候群及克雷格症候群病人
  (FDA-approved indications: treatment of seizures in patients ⩾ 2 years of age with Dravet sx or Lennox-Gastaut sx)
- 屬5級管制藥品：DEA US (drug enforcement Administration) schedule: V
- 每cc有100毫克，每瓶100cc，草莓口味。Dosage form: 100 mg/ml oral solution (strawberry flavored)
- 劑量Dosing: initial 2.5 mg/kg twice daily (5 mg/kg/d), titrated at weekly intervals to minimum effective dose or
  10 mg/kg twice daily (20 mg/kg/d)
- 肝功能異常者需調整劑量 (Dosage adjustment needed in hepatic impairment)
- 不要突然停藥 (Do not abruptly discontinue)
- 可以空腹或與食物一起服用 (Administration: administer consistently with or without food)
- 主要藥物交替作用包括福利寧、帝拔癲、 CYP3A4 & CYP2C19 誘導及抑制劑、中樞神經系統抑制劑
  (Primary drug-drug interactions: clobazam, valproates, CYP3A4 & CYP2C19 inducers & inhibitors, CNS depressants)
- 常見不良反應包括失眠、腹瀉、食慾降低及肝功能指數上升
  (Common adverse events: somnolence, diarrhea, decreased appetite, elevated hepatic transaminases)
- 吃藥前需驗肝功能指數及黃疸值，並在開始吃藥後第1, 3, 6 個月監測肝指數及黃疸值
  (Monitoring: AST/ALT and total bilirubin at baseline and 1, 3, and 6 months after initiation and 1 month following
  dosing changes and/or addition of medications affecting liver function
- Product distribution: available via limited distribution (i.e., specialty pharmacy)
- Manufacturer's estimated annual list price: USD 32,500

Chen JW et al. Ann Pharmacother 2019;53:603-611

Clinical handling of CBD

- Start low (2.5 or 5 mg/kg/day), increase to 10mg/kg after 2 weeks
- Review clinical response and adverse effects on 10 mg/kg/day
- Remain on this dose if effective
- Otherwise increase dose in steps of 5 mg/kg/fay if CBD is well tolerated
- Stop at 20-25 mg/kg/day – withdraw CBD if ineffective

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肝功能異常
Hepatic impairment

肝功能異常 (Hepatic impairment)	起始劑量 (Starting dose)	維持劑量 (Maintenance dose)	最大建議劑量 (Maximum recommended dose)
輕度 (Mild)	2.5 mg/kg BID (5 mg/kg/day)	5 mg/kg twice daily (10 mg/kg/day)	10 mg/kg twice daily (20 mg/kg/day)
中度 (Moderate)	1.25 mg/kg BID (2.5 mg/kg/day)	2.5 mg/kg BID (5 mg/kg/day)	5 mg/kg BID (10 mg/kg/day)
重度 (Severe)	0.5 mg/kg BID (1 mg/kg/day)	1 mg/kg BID (2 mg/kg/day)	2 mg/kg BID (4 mg/kg/day)*

* Higher doses of cannabidiol may be considered in patients with severe hepatic impairment where the potential benefits outweigh the risks

不良反應 (Tabulated list of adverse reactions)

System Organ Class	Frequency	Adverse reactions from clinical trials
• 感染 (Infections and infestations)	• 常見 (Common)	• 肺炎氣管炎鼻咽炎泌尿道感染 (Pneumonia, bronchitis, nasopharyngitis, urinary tract infection)
• 代謝及營養障礙 (Metabolism and nutrition disorders)	• 非常常見 (Very common) • 常見 (Common)	• 食慾降低 (Decreased appetite) • 食慾增加 (Increased appetite)
• 精神疾病 (Psychiatric disorders)	• 常見 (Common)	• 躁動、失眠、異常行為、攻擊性、異常行為 Irritability, insomnia, aggression, abnormal behaviour, agitation
• 神經系統疾病 (Nervous system disorders)	• 非常常見 (Very common) • 常見 (Common)	• 失眠 Somnolence • 想睡、流口水、顫抖 Lethargy, drooling, tremor
• 呼吸胸腔及橫膈膜疾病 (Respiratory, thoracic and mediastinal disorders)	• 常見 (Common)	• 咳嗽 Cough
• 腸胃道疾病 (Gastrointestinal disorders)	• 非常常見 (Very common)	• 腹瀉、嘔吐 (Diarrhoea, vomiting)
• 肝膽疾病 (Hepatobiliary disorders)	• 常見 (Common)	• 肝功能指數上升 (AST increased, ALT increased, GGT increased, liver function test abnormal)
• 皮膚及皮下組織疾病 (Skin and subcutaneous tissue disorders)	• 常見 (Common)	• 皮疹 (Rash)
• 全身疾病 (General disorders and administration site conditions)	• 非常常見 (Very common)	• 發熱、疲倦 (Pyrexia, fatigue)
• 調查 (Investigations)	• 常見 (Common)	• 體重減輕 (Weight decreased)

- 非常常見 Very common (≧1/10),常見common (≧ 1/100 to < 1/10), 不常見uncommon (≧ 1/1,000 to < 1/100)

謝謝您們的聆聽