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学位授与の要件	富山大学学位規則第３条第３項該当
教　育　部　名	富山大学大学院医学薬学教育部　博士後期課程 薬科学専攻
学位論文題目	Chemical constituents and anti-pancreatic cancer activities of selected Thai medicinal plants （選択されたタイ産薬用植物の化学成分と抗膵臓がん活性）

論文審査委員

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Chemical constituents and anti-pancreatic cancer activities of selected Thai medicinal plants

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Cancer continues to be a major health problem worldwide, accounting for nearly 10 million deaths in 2020. Among all types of cancer, pancreatic cancer is the deadliest, having the mortality rate nearly equivalent to the incidence rate. The incidence of pancreatic cancer continues to increase throughout the world, and is projected as the third leading cause of cancer death by 2025. Pancreatic cancer is mostly asymptomatic at the initial stage, and most pancreatic cancer patients are diagnosed in an advanced stage when the tumor has already metastasized to distant organs, making surgery almost impossible. Even the early-stage patients usually suffer from the disease recurrence within a year after surgical tumor removal. Chemotherapy is used to extend survival and/or relieve pancreatic cancer patients' symptoms. However, pancreatic tumors have an intrinsic resistance to almost all the clinically used chemotherapeutic agents. Therefore, there is an urgent need to find new effective agents against pancreatic cancer.

Pancreatic tumor in general shows hypovascularity with abundant fibrous stroma, leading to critical gradient of the nutrition supply within tumor microenvironment. However, pancreatic tumor cells have an inherent ability to adapt such stressed (austere) conditions by altering their energy metabolism, and gaining tolerance to nutrition starvation, a phenomenon known as "austerity" in cancer biology. The search of agents that inhibit cancer cells tolerance to nutrition starvation is a promising approach for the anticancer drug discovery.

In the present study, extracts of 24 selected Thai indigenous medicinal plants extracts were tested for their preferential cytotoxic activity (antiausterity activity) against PANC-1 human pancreatic cancer cell line in nutrient-deprived medium (NDM) and standard nutrient-rich medium (DMEM). Among the tested plants, five extracts exhibited promising activities. These include *Piper ribesoides* (PC_{50} = 24 μg/mL), *Citrus hystrix* (PC_{50} = 8.9 μg/mL), *Kaempferia parviflora* (PC_{50} = 3.3 μg/mL), *Derris scandens* (PC_{50} = 0.8 μg/mL), and *Boesenbergia pandurata* (PC_{50} = 0.5 μg/mL). The phytochemical investigation of these active extracts was carried out in order to identify the active constituents and elucidated the molecular mechanism.

1. Chemical constituents of *Kaempferia parviflora* and their antiausterity activity

Phytochemical investigation of *K. parviflora* extract led to the isolation of fourteen compounds, including two polyoxygenated cyclohexanes (**1** and **2**), eleven flavonoids (**3**–**13**), and *β*-sitosterol (**14**) (Chart 1). X-ray analysis was performed for compound **1** (Figure 1). All isolated compounds were tested for their preferential cytotoxicity against PANC-1 cells. Among them, 5-hydroxy-7-methoxyflavone (**3**) displayed the most potent activity with a PC_{50} value of 0.8 μM. It was also found to inhibit PANC-1 cancer cell colony formation in DMEM (Figure 2).[1]

2. Chemical constituents of *Citrus hystrix* and their antiausterity activity

Phytochemical investigation of *Citrus hystrix* extract led to the isolation of 10 coumarins (**15**−**24**) (Chart 2) including a new furanocoumarin named (*S*)-(−)-2′-methoxyoxypeucedanin hydrate (**15**). The absolute configuration of **15** was determined by comparing the $[\alpha]_D$ and ECD spectral data with those of (*R*)-(+)-oxypeucedanin hydrate (**17**) (Figure 3). All isolated compounds were tested for their preferential cytotoxicity against three human pancreatic cancer cell lines. Among these, bergamottin (**21**) was identified as the most active constituent. A real-time live cell imaging experiment revealed that compound **21** could induce cell shrinkage, membrane blebbing, and disintegration of organelles in PANC-1 cells. Bergamottin (**21**) was also found to inhibit PANC-1 cell migration and colony formation (Figure 4).[2]

3. Chemical constituents of *Derris scandens* and their antiausterity activity

Phytochemical investigation of *Derris scandens* extract led to the isolation of four prenylated isoflavones (**25**–**28**) (Chart 3) including a new compound named 4′-*O*-methylgrynullarin (**25**). The structure elucidation of the new compound was achieved by HRFABMS and NMR spectroscopic analysis (Figure 5). The isolated compounds exhibited potent antiausterity activity against PANC-1 human pancreatic cancer cell line under nutrient-deprived conditions. The new compound 4′-*O*-methylgrynullarin (**25**) was also found to inhibit PANC-1 cell migration and colony formation under nutrient-rich condition (Figure 6 and 7). Mechanistically, compound **25** inhibited key survival proteins in the Akt/mTOR signaling pathway in NDM (Figure 8).[3]

4. Chemical constituents of *Piper ribesoides* and their antiausterity activity

Phytochemical investigation of *Piper ribesoides* extract led to the isolation of six compounds (**14**, **29**−**33**) (Chart 4), including two new polyoxygenated cyclohexane derivatives, named ribesoidones A and B (**29** and **30**). The structural elucidation of the new compounds was achieved by a combination of HREIMS, NMR, and ECD spectroscopic analyses (Figure 9 and 10). Isolated compounds were tested for their antiausterity activity against PANC-1 human pancreatic cancer cell line. Among these, compounds **29**, **30** and **31** displayed potent preferential cytotoxic activity with PC_{50} values of 5.5–7.2 μM. Ribesoidone A (**29**) was also found to inhibit PANC-1 colony formation under normal nutrient-rich conditions (Figure 11).[4]

5. Chemical constituents of *Bosenbergia pandurata* and their antiausterity activity

Phytochemical investigation of *Bosenbergia pandurata* extract led to the isolation of five compounds (**34**−**37**) (Chart 5). All isolated compounds were tested for their preferential cytotoxicity against PANC-1 and MIA PaCa-2 human pancreatic cancer cell lines where most compounds exhibited potent activities (Table 1). (+)-Panduratin A (**34**) and geranyl-2,4-dihydroxy-6-phenethylbenzoate (**37**) were also found to inhibit PANC-1 cell migration (Figure 12) and colony formation in normal nutrient-rich condition (Figure 13 and 14). Mechanistically, these two compounds inhibited Akt/mTOR and autophagy signaling pathway, leading to selective PANC-1 cancer cell death under the nutrition starvation condition (Figure 15 and 16).[5,6] Moreover, (+)-isopanduratin A (**35**) was found to inhibit MIA PaCa-2 cell migration and colony formation in normal nutrient-rich condition. Mechanistically, it inhibited Akt/mTOR and autophagy survival signaling pathway in MIA PaCa-2 cells. (+)-Isopanduratin A (**35**) was also found to strongly suppress the MIA PaCa-2 tumor growth in a xenograft mouse model.[7]

6. Conclusion

Phytochemical investigation of five selected Thai medicinal plant extracts led to the isolation of **37** compounds including four new compounds. Among isolated compounds **3**, **21**, **25**, **29**, **34**, **35**, and **37** displayed the potent antiausterity activities. These compounds were studied for their anti-metastatic potential by employing a real-time cell migration and colony formation inhibition studies, and provided unbiased quantitative information of the effect of the tested compounds against pancreatic cancer cell motility, as evidenced by real-time movies. Mechanistically, compounds **25**, **34**, **35**, and **37** were found to inhibit the key survival proteins in the Akt/mTOR signaling pathway. In turn, isopanduratin A (**35**) was investigated for its *in vivo* anti-tumor activity against MIA PaCa-2 human pancreatic tumor xenograft in nude mice, and showed remarkable reduction of tumor over the period of 29 days study, with no toxicity at the administered dose. In summary, the current research led to the discovery of diverse natural product leads for the drug development against pancreatic cancer.

References

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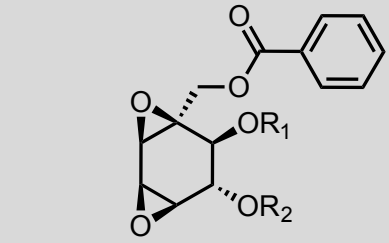
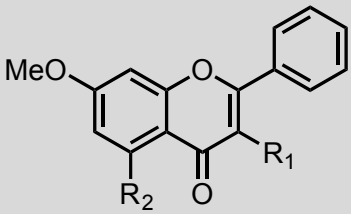
2. **Sijia Sun**, Ampai Phrutivorapongkul, Dya Fita Dibwe, Chandrasekar Balachandran and Suresh Awale. Chemical constituents of Thai *Citrus hystrix* and their antiausterity activity against the PANC-1 human pancreatic cancer cell line. *Journal of Natural Products*, **2018**, *81*, 1877–1883.
3. **Sijia Sun,** Dya Fita Dibwe, Min Jo Kim, Ashraf M. Omar, Nguyen Duy Phan, Haruka Fujino, Nusrin Pongterdsak, Kritsaya Chaithatwatthana, Ampai Phrutivorapongkul and Suresh Awale. A new anti-austerity agent, 4'-*O*-methylgrynullarin from *Derris scandens* induces PANC-1 human pancreatic cancer cell death under nutrition starvation *via* inhibition of Akt/mTOR pathway. *Bioorganic & Medicinal Chemistry Letters*, **2021**, *40*, 127967.
4. **Sijia Sun**, Ashraf M. Omar, Min Jo Kim, Nguyen Duy Phan, Yaowared Chulikhit and Suresh Awale. Chemical constituents of Thai *Piper ribesoides* and their antiausterity activities against the PANC-1 human pancreatic cancer cell line. *Fitoterapia*, **2021**, *151*, 104901.
5. **Sijia Sun**, Min Jo Kim, Ashraf M. Omar, Nguyen Duy Phan and Suresh Awale. (+)-Panduratin A induces PANC-1 human pancreatic cancer cell death preferentially under nutrient starvation by inhibiting PI3K/Akt/mTOR/autophagy signaling pathway. *Phytomedicine Plus*, **2021**, *1*(4),100101.
6. **Sijia Sun**, Min Jo Kim, Ashraf M. Omar, Nguyen Duy Phan, Mio Aoike and Suresh Awale. GDP induces PANC-1 human pancreatic cancer cell death preferentially under nutrient starvation by inhibiting PI3K/Akt/mTOR/Autophagy signaling pathway. *Chemistry and Biodiversity*, **2021**, *81*, e2100389.
7. **Sijia Sun**, Suresh Awale et al. *In vivo* anti-tumor effect of isopanduratin A against MIA PaCa-2 human pancreatic cancer xenograft model. **2021**. *In preparation.*

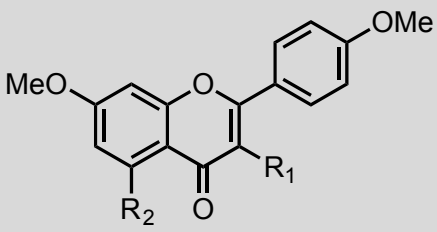
Chart 1. Structures of compounds isolated from *K. parviflora*



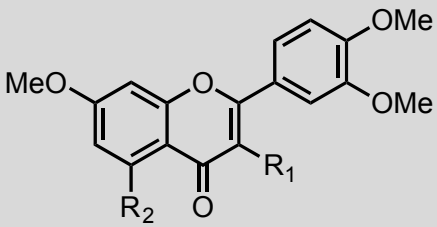
1 R_1 = H, R_2 = COMe
2 R_1 = COMe, R_2 = H



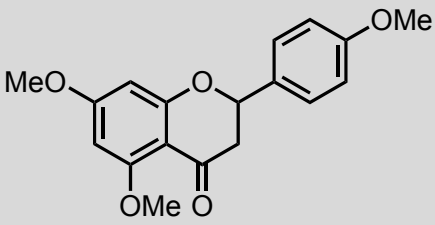
3 R_1 = H, R_2 = OH
4 R_1 = OMe, R_2 = OH
5 R_1 = H, R_2 = OMe
6 R_1 = OMe, R_2 = OMe



7 R_1 = H, R_2 = OH
8 R_1 = OMe, R_2 = OH
9 R_1 = H, R_2 = OMe
10 R_1 = OMe, R_2 = OMe



11 R_1 = OMe, R_2 = OH
12 R_1 = OMe, R_2 = OMe



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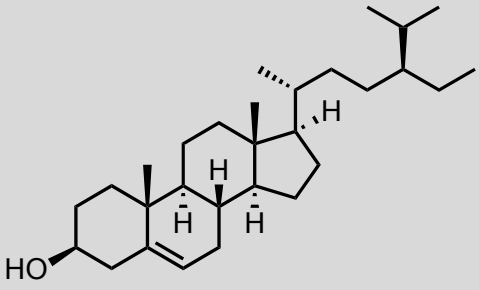

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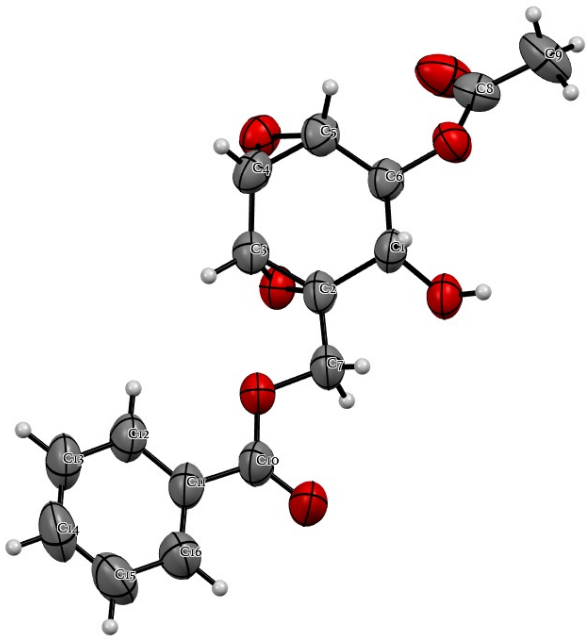


Figure 1. Anisotropic displacement ellipsoid plot of $C_{16}H_{16}O_7$ at the 70% probability level.

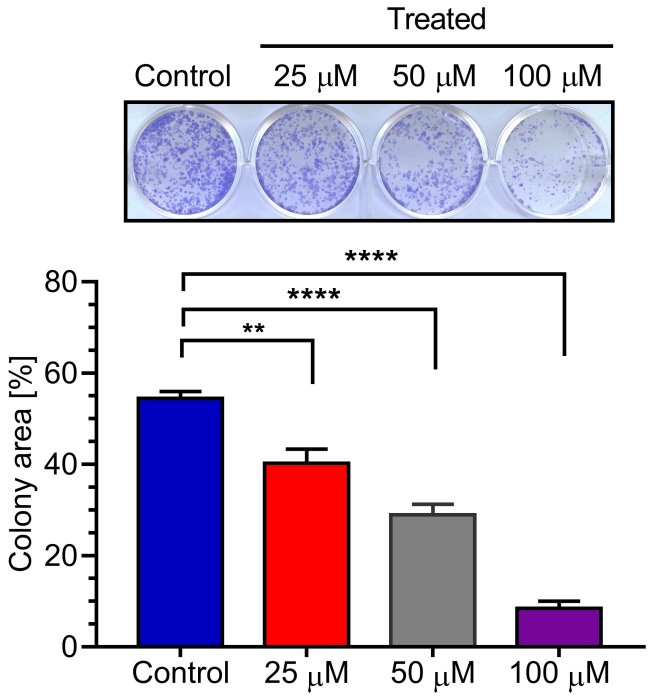
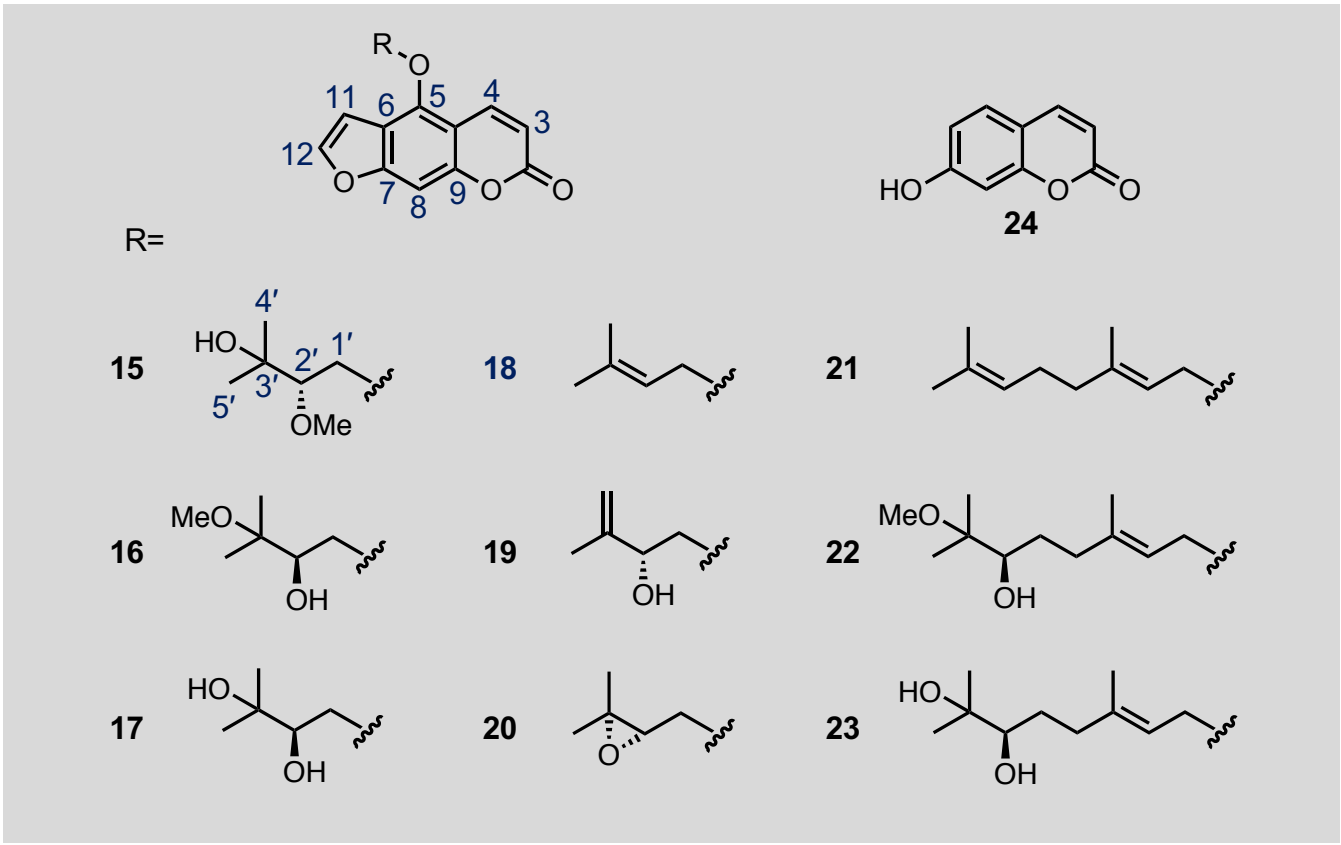


Figure 2. Effect of 5-hydroxy-7-methoxyflavone (**3**) on PANC-1 colony formation

Chart 2. Structures of compounds isolated from *C. hystrix*



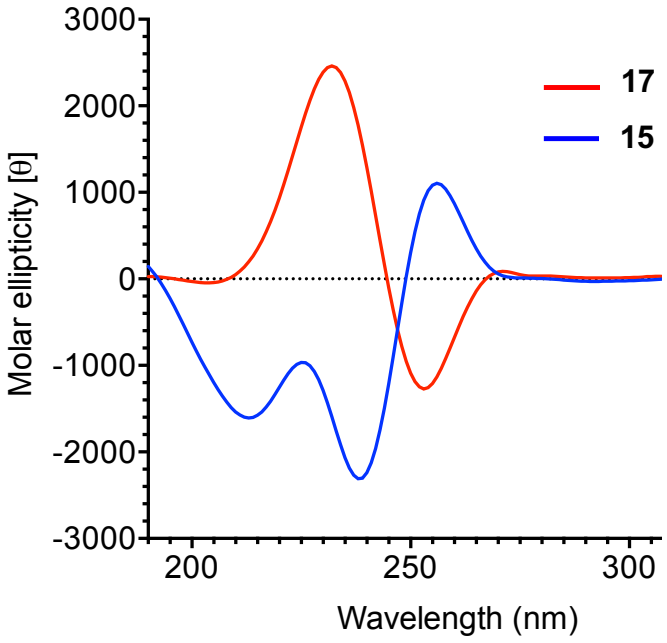


Figure 3. ECD spectra for compounds **15** and **17**.

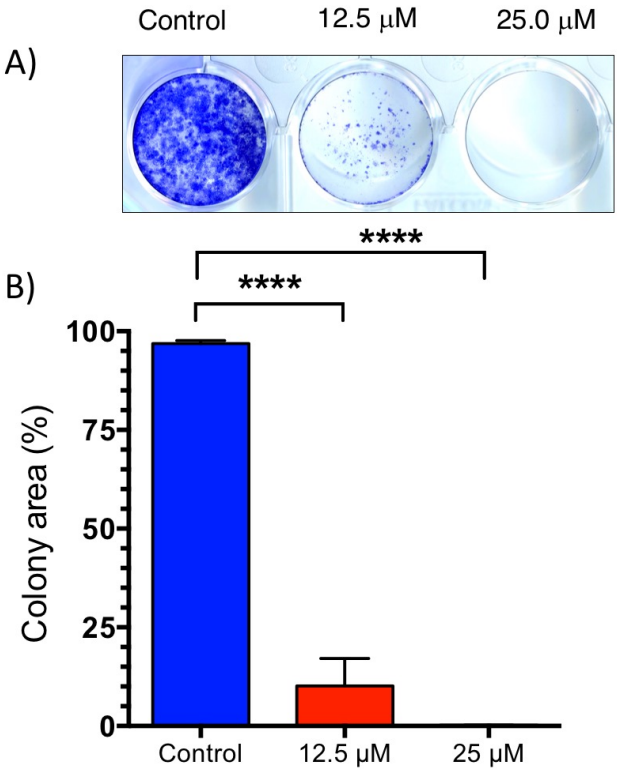
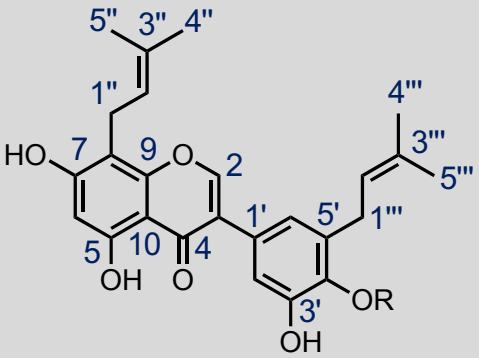
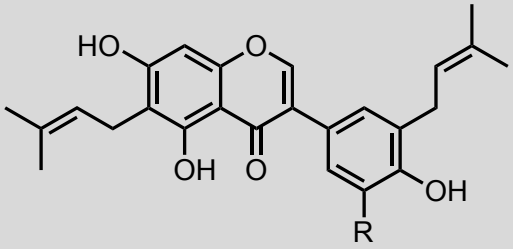


Figure 4. Effect of bergamottin (**21**) on PANC-1 cells colony formation.

Chart 3. Structures of compounds isolated from *D. scandens*



25 R = CH_3
28 R = H



26 R = OH
27 R = H

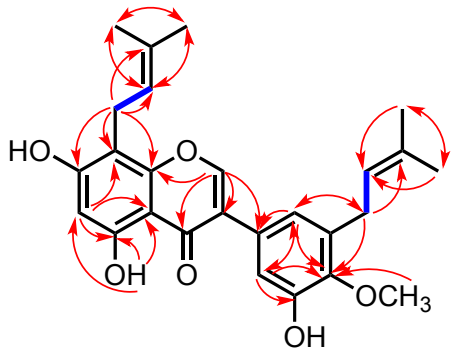


Figure 5. Connectivities (bold lines) deduced by the COSY and HMQC spectra and significant HMBC correlations (solid arrows) in **25**.

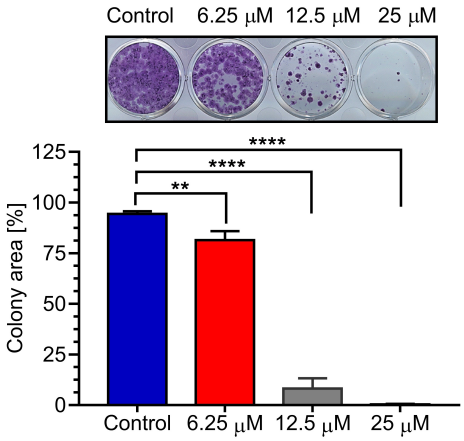


Figure 6. Effect of 4′-*O*-methylgrynullarin (**25**) on PANC-1 cells colony formation.

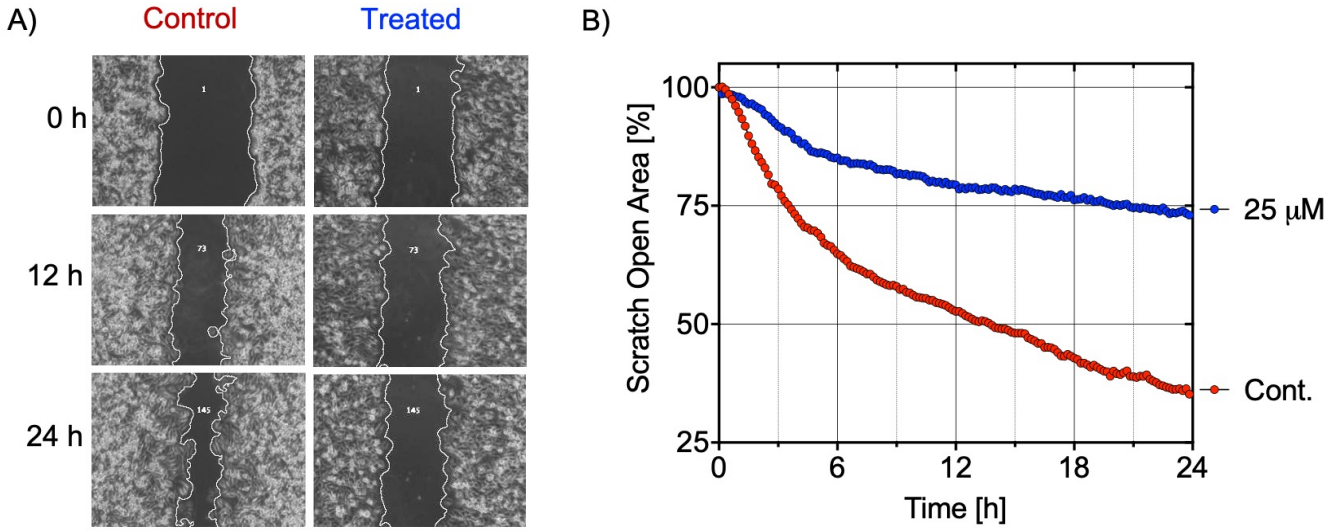


Figure 7. Compound **25** suppresses the migration of PANC-1 in a wound-healing assay in real-time.

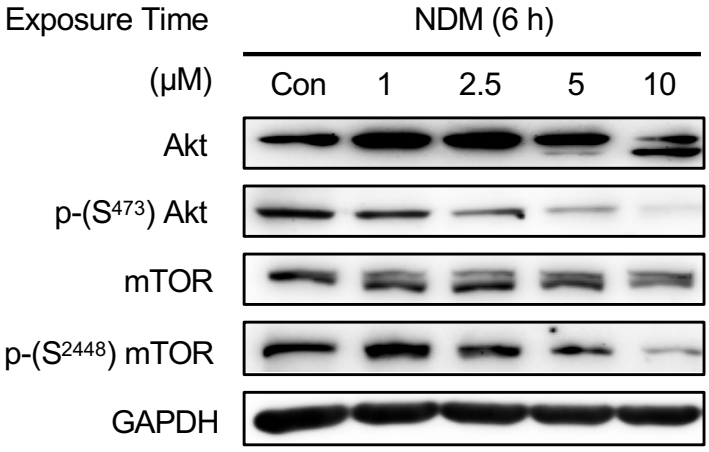
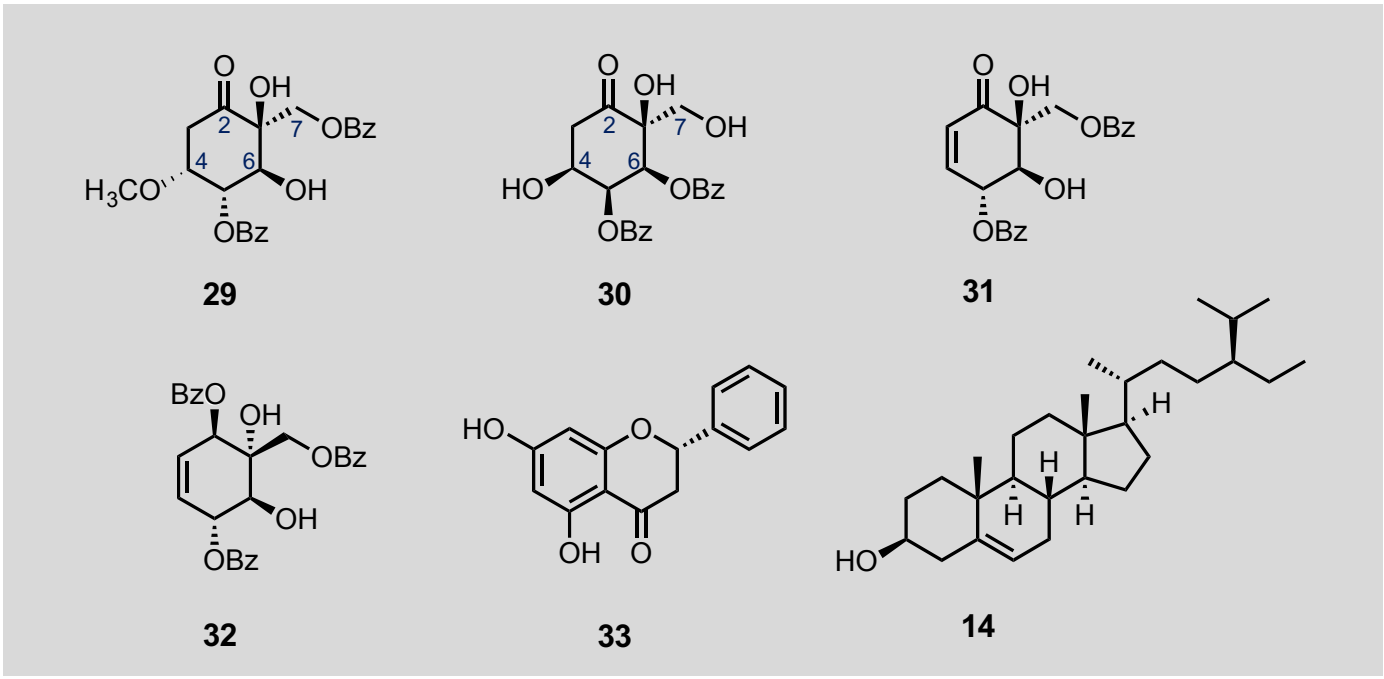


Figure 8. Effect of 4′-*O*-methylgrynullarin (**25**) on the key proteins involved in Akt/mTOR signaling in PANC-1 cells.

Chart 4. Structures of compounds isolated from *P. ribesoides*



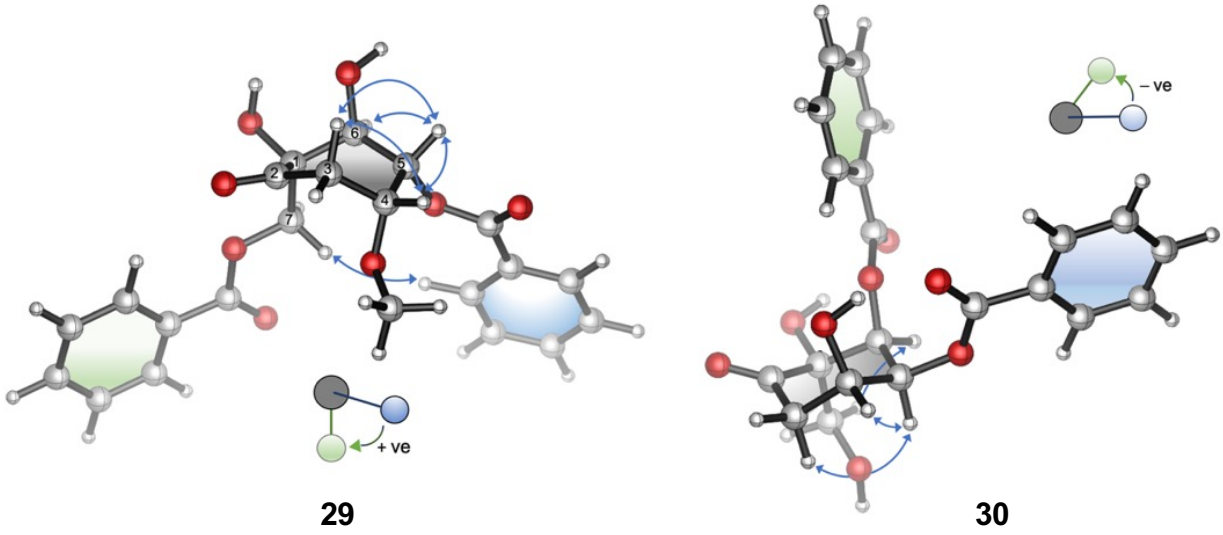


Figure 9. Key NOESY correlations (blue arrows) in **29** and **30** and sign of exciton chirality.

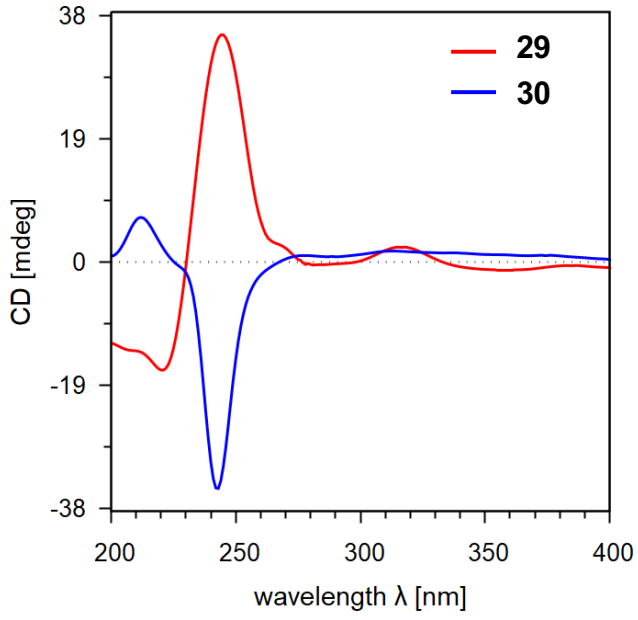


Figure 10. Experimental ECD spectra for compounds **29** and **30**.

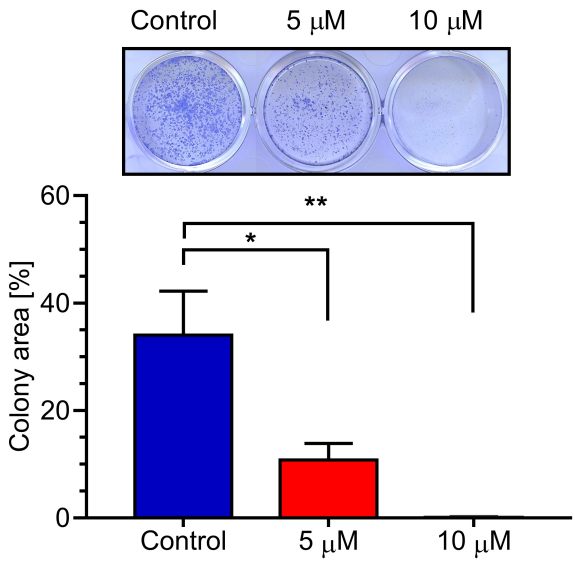


Figure 11. Effect of **29** on PANC-1 cells colony formation.

Chart 5. Structures of compounds isolated from *B. pandurata*

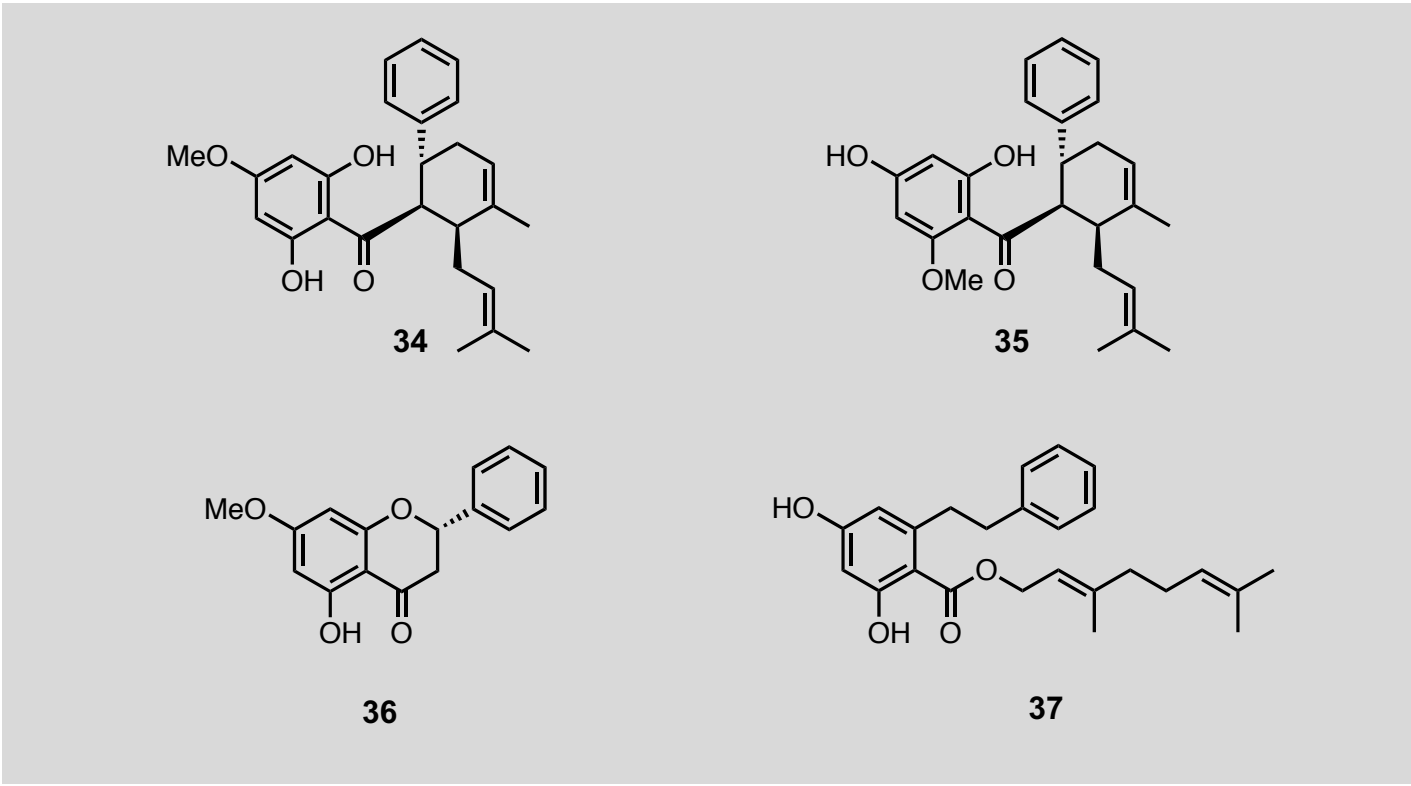


Table 1. Anti-austerity activity (PC_{50}) [b] of the compounds against two human pancreatic cancer cell lines.

Cell lines	**34**	**35**	**36**	**37**	Arct.[a]
PANC-1	1.6	0.9	73	10	0.7
MIA PaCa-2	0.3	0.2	>100	4.8	1.9

[a] Positive control, Arctigenin.

[b] [PC_{50}]: Concentration at which 50% cells were killed preferentially under nutrient nutrient-deprived condition (NDM) but non-cytotoxic under ordinary nutrient rich condition (DMEM) at 24 h.

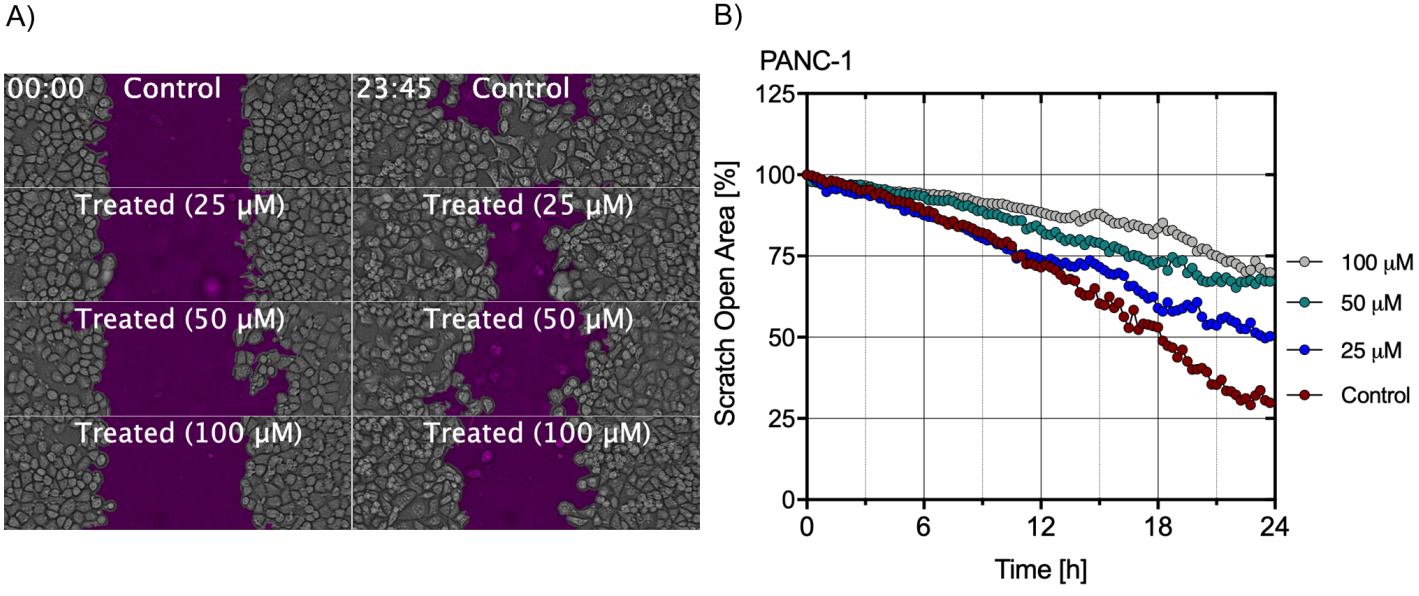


Figure 12. Compound **37** suppresses the migration of PANC-1 in a wound-healing assay in real-time.

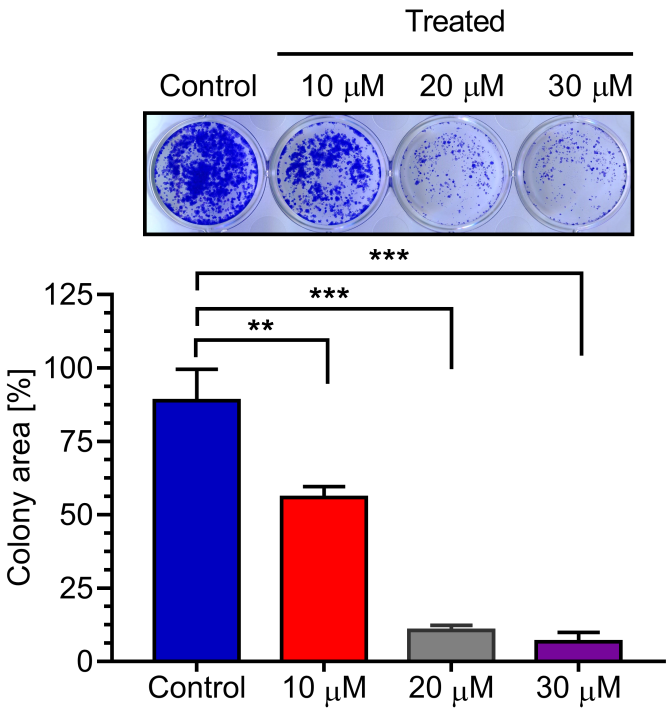


Figure 13. Effect of **34** on PANC-1 cells colony formation.

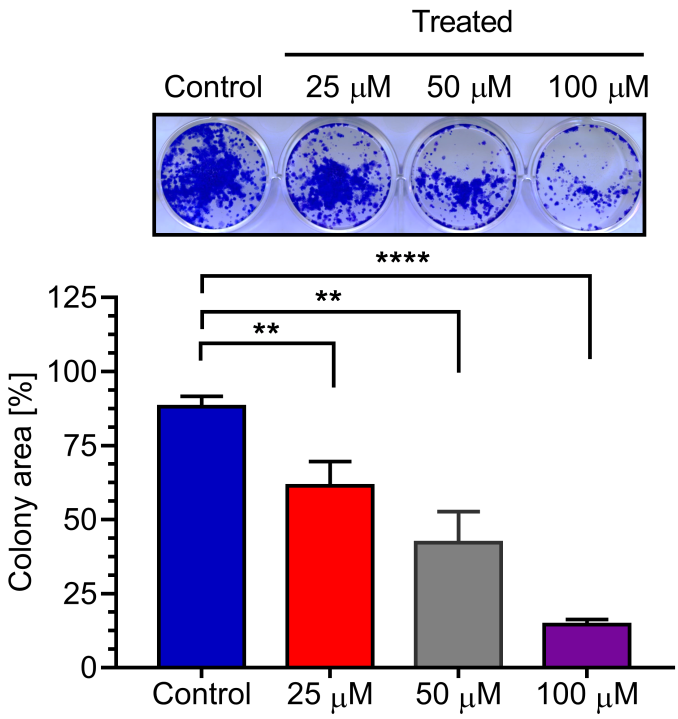


Figure 14. Effect of **37** on PANC-1 cells colony formation.

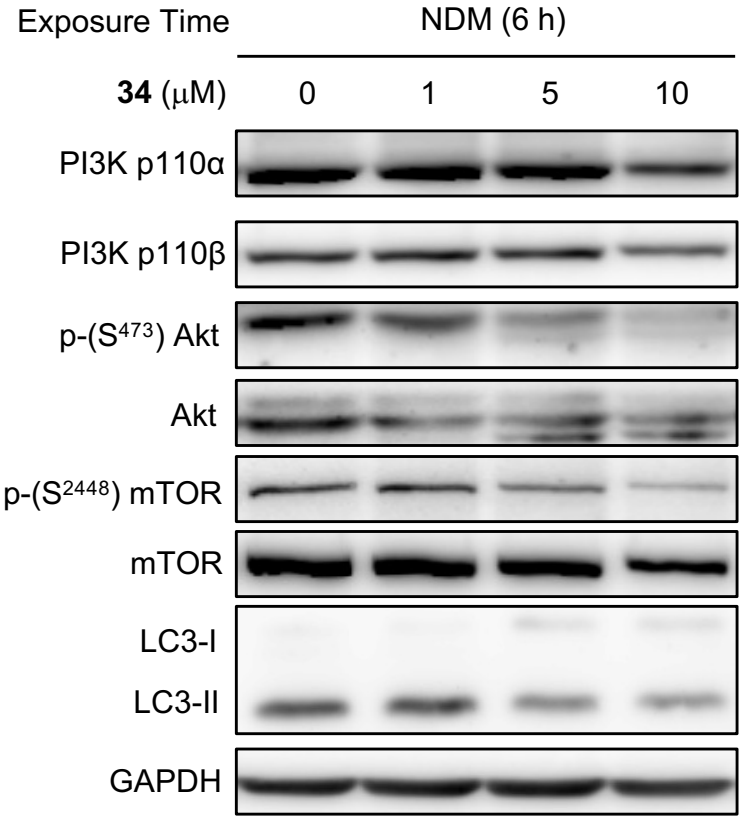


Figure 15. Effect of **34** on the key proteins involved in PI3K/Akt/mTOR/autophagy signaling in PANC-1 cells.

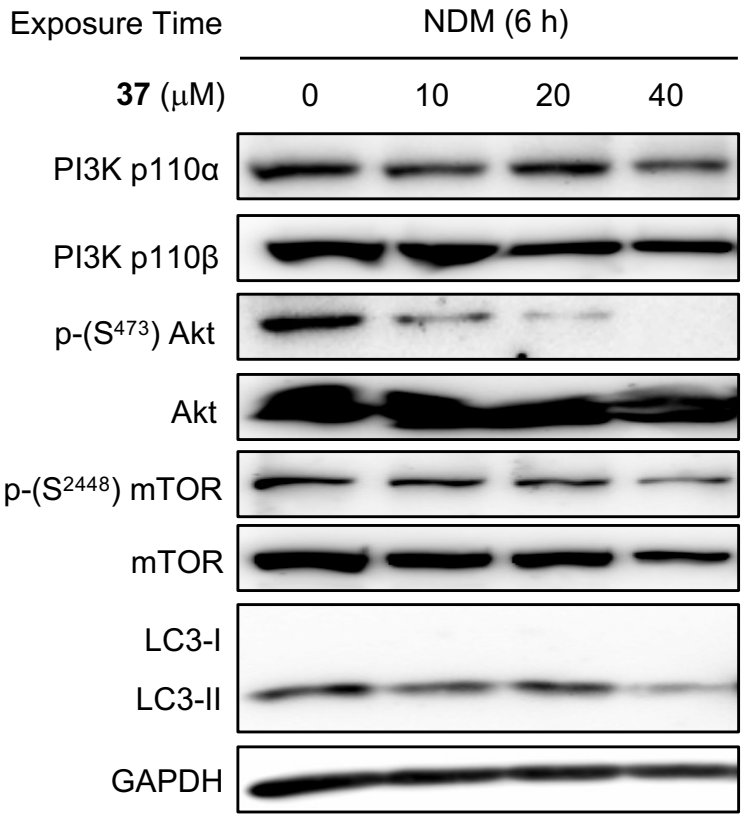


Figure 16. Effect of **37** on the key proteins involved in PI3K/Akt/mTOR/autophagy signaling in PANC-1 cells.

様式７

学位論文審査の要旨

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	（副査）　准教授	田浦　太志	
	（副査）　准教授	スレス　アワレ	

（論文題目）

Chemical constituents and anti-pancreatic cancer activities of selected Thai medicinal plants（選定されたタイ産薬用植物の化学成分と抗膵臓がん活性）

（判定）

合格

（論文審査の要旨）（２頁以内）

膵臓がんは、がんの中でも最も死亡率の高いがんで、死亡率は罹患率とほぼ同等となっている。膵臓がんの発生率は世界的に増加し続けており、2030年にはがんによる死亡原因の第3位になると予測されている。膵臓がんは、初期段階では自覚症状がない場合が多く、腫瘍が発見された時には、腫瘍が遠隔臓器に転移してしまったため、治療が極めて困難な場合が多い。さらに早期発見の場合でも、手術で腫瘍を取り除いた後、1年以内に再発してしまうことがほとんどである。抗がん剤を用いた化学療法は、膵臓がん患者の生存期間の延長や症状の緩和を目的として行われるが、膵臓がんは臨床応用されているほとんど全ての化学療法剤に対して耐性を有している。そのため、膵臓がんに有効な新しい薬剤を見出すことは、喫緊の課題となっている。膵臓腫瘍は、一般的に血管が少なく、繊維質の間質が豊富であるため、腫瘍微小環境内の栄養供給に大きな勾配が生じている。しかし、膵臓の腫瘍細胞の場合は、エネルギー代謝を変化させることでこのようなストレス（緊迫）状態に適応し、栄養飢餓に対する耐性を獲得する能力を有している。そのため、がん細胞の栄養飢餓に対する耐性を阻害する薬剤の探索は、膵臓がん治療薬発見のための有望なアプローチとなっている。本研究では、厳選されたタイ固有の薬用植物24種の抽出物について、栄養欠乏培地（NDM）および栄養豊富な標準培地（DMEM）を用いて、ヒト膵臓がん細胞株PANC-1に対する細胞毒性活性（antiausterity活性）を調査した。その結果、5種類の植物に有望な活性が見出された（*Piper ribesoides* (PC_{50} = 24 μg/mL), *Citrus hystrix* (PC_{50} = 8.9 μg/mL), *Kaempferia parviflora* (PC_{50} = 3.3 μg/mL), *Derris scandens* (PC_{50} = 0.8 μg/mL), *Boesenbergia pandurata* (PC_{50} = 0.5 μg/mL)）。そこで、これらの活性抽出物について詳細な調査を行い、活性成分の同定と分子メカニズムの解明を行った。

1. *Kaempferia parviflora* の化学成分と PANC-1 ヒト膵臓がん細胞株に対する antiausterity 活性

K. parviflora 抽出物の化学成分調査により、2 種類のポリオキシ化シクロヘキサン類（**1** および **2**）、11 種類のフラボノイド（**3–13**）、およびβ-シトステロール（**14**）を含む 14 種類の化合物が単離された。単離した化合物の PANC-1 細胞に対する細胞毒性を調べた結果、5-hydroxy-7-methoxyflavone（**3**）が最も強い活性を示し、PC_{50} 値は 0.8μM であった。また、DMEM を用いた PANC-1 細胞のコロニー形成を阻害することも確認された。

2. *Citrus hystrix*の化学成分とPANC-1ヒト膵臓がん細胞株に対するantiausterity活性

Citrus hystrix の抽出物の化学成分調査により、新規なフラノクマリン誘導体である (*S*)-(-)-2′-methoxyoxypeucedanin hydrate（**15**）を含む10種類のクマリン類（**15–24**）が単離された。**15**の絶対配置は、(*R*)-(+)-oxypeucedanin hydrate（**17**）の比旋光度およびECDスペクトルデータと比較して決定した。単離された化合物のうち、bergamottin（**21**）が最も活性の高い成分であることが確認された。また、ライブセルイメージング実験により、化合物**21**はPANC-1細胞に対して、細胞収縮、膜の剥離、オルガネラ崩壊を誘発することが明らかになった。さらに、PANC-1細胞の遊走やコロニー形成を阻害することも確認された。

3. *Derris scandens*の化学成分とPANC-1ヒト膵臓がん細胞株に対するantiausterity活性

*Derris scandens*の抽出物の化学成分調査により、4′-*O*-methylgrynullarin（**25**）という新規化合物を含む4つのプレ

ニル化イソフラボン類（**25**−**28**）が単離された。この新規化合物の構造は、HRFABMSおよびNMRスペクトル分析によって解明された。単離された化合物は、栄養飢餓条件下で、PANC-1ヒト膵臓がん細胞株に対して強力なantiausterity活性を示した。また、新規化合物4′-*O*-methylgrynullarin（**25**）は、通常の栄養豊富な条件下でPANC-1細胞の遊走とコロニー形成を阻害することが分かった。メカニズム解析の結果、化合物**25**はAkt/mTORシグナル伝達経路の主要なタンパク質を阻害することも明らかとなった。

4. *Piper ribesoides*の化学成分とPANC-1ヒト膵臓がん細胞株に対するantiausterity活性

*Piper ribesoides*の抽出物の化学成分調査により、2つの新規なポリオキシ化シクロヘキサン誘導体を含む6つの化合物（**14**, **29**−**33**）が単離され、新規化合物についてはribesoidone AおよびBと命名された（**29**および**30**）。これらの化合物の構造は、HREIMS、NMR、ECDを組み合わせた分光分析によって明らかにされた。単離された化合物のうち、化合物**29**、**30**、**31**は強力な細胞毒性を示した（PC_{50}値：5.5〜7.2 μM）。また、ribesoidone A（**29**）は、通常の栄養豊富な条件下でPANC-1のコロニー形成を阻害することが分かった。

5. *Bosenbergia pandurata*の化学成分とPANC-1ヒト膵臓がん細胞株に対するantiausterity活性

*Bosenbergia pandurata*の抽出物の化学成分調査により、5つの化合物が単離された（**34**−**37**）。単離された化合物について、PANC-1およびMIA PaCa-2ヒト膵臓がん細胞株に対するantiausterity活性を評価した。その結果、(+)-Panduratin A（**34**）、geranyl-2,4-dihydroxy-6-phenethylbenzoate（**37**）、およびisopanduratin A（**35**）が、栄養飢餓状態でAkt/mTORとオートファジーのシグナル伝達経路を阻害し、PANC-1を選択的に細胞死させることが分かった。さらに、isopanduratin A（**35**）のin vivo抗腫瘍活性を調べたところ、異種移植モデルのMIA PaCa-2腫瘍細胞増殖を強く抑制することが確認された。

以上本研究では、5種類のタイ産薬用植物の抽出物から、4つの新規化合物を含む37の化合物が単離された。分離された化合物のうち、**3**、**21**、**25**、**29**、**34**、**35**、**37**は強力なantiausterity活性を示した。これらの化合物の抗転移能については、リアルタイムの細胞移動およびコロニー形成阻害試験にて検討され、その可能性について有用な情報を得ている。また、これらの化合物の作用機序を調べたところ、化合物**25**、**34**、**35**、**37**は、Akt/mTORシグナル経路の主要なタンパク質を阻害することが示唆された。活性化合物のうち、isopanduratin A（**35**）については、ヌードマウスを用いたin vivo抗腫瘍活性評価も実施され、顕著な毒性なしに強力なin vivo抗腫瘍活性を示すことが確認された。以上のように、今回の研究では、膵臓がんの治療薬開発のための多様な天然物リード化合物を発見することに成功しており、今後の膵臓がん治療戦略への展開に大きく貢献する研究成果と評価できる。

主査および副査は、申請者Sijia Sun 氏に面接と共に論文内容について審査を行い、博士（薬科学）の学位を授けるに値すると判定した。

（学位論文のもとになる論文　著者名, 論文題目, 掲載誌名, 巻, 最初の頁と最後の頁, 年を記載）

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