Session 9
Natural Product III
Biosynthesis, Modification, Chemical Library & Novel New Usage

Chairperson:

Jarupa Viyoch, Naresuan University

Co-Chair:

Shiow-Ju Lee, National Health Research Institutes

Panelists:

Nuntika Prommee, Naresuan University

Shu-Ling Fu, National Yang Ming Chiao Tung University

Summary

- 10 from 20 abstracts were selected for oral presentation
- The selected abstracts can be divided into 5 categories, including
    1) Synthesis : 1 abstract
    2) Modification : 2 abstracts
    3) Impurity identification : 1 abstract
    4) Extraction process : 1 abstract
    4) New usage and/or Mechanism(s) clarification : 5 abstracts

Synthesis

Design and Synthesis of Patentiflorin A Analogs as Novel Antiviral Agents

NO-9-13

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Objective: Design and synthesize glycosylated arylnaphthalene lignans (ANLs) based on Patentiflorin A as broad-spectrum antiviral agents.

Method: Synthesized 10 glycosylated-ANLs by conjugating sugar moieties onto the diphyllin scaffold; structures confirmed by Q-TOF MS and NMR.

Cytotoxicity: IC50 values in A549 cells ranged from 0.033 to 0.25 μM.

Antiviral activity: Screened against pseudoviruses (VSVpp, H5N1pp, and other pandemic-relevant viruses); lead compound **DIA1-5** showed potent activity with selectivity indices of 132 (FIPVpp) and 259 (ZIKVpp).

Conclusion: Findings advance structure-activity relationship (SAR) understanding of ANLs, supporting future broad-spectrum antiviral drug development.

Modification 1

Design, Synthesis, and Evaluation of Novel Andrographolide Derivatives as Anti-Pancreatic Cancer Therapeutics

NO-9-11

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Background: Pancreatic cancer (PDAC) has limited treatment options; mutant p53 (e.g., R273H) is a potential target, but Andrographolide's efficacy is limited at high concentrations.

Objective: Develop Andrographolide derivatives with improved anti-pancreatic cancer activity.

Methods: Tested cytotoxicity, proliferation/migration, p53 expression, molecular docking, and in vivo efficacy in a PDAC xenograft model.

Results: Compound 4 showed the strongest anticancer effect, suppressing mutant p53 expression and inhibiting PANC-1 growth/migration in a dose- and time-dependent manner. It also acted as a stable fluorescent probe, binding p50/NF-κB, and reduced tumor growth in vivo.

Conclusion: Compound 4 is a dual-function molecule with both anticancer activity and utility as a fluorescent probe for target identification.

Modification 2

Development of Natural Antioxidant Pigments from Caesalpinia sappan L. Using Clay Mineral Adsorption: Functional Colorants for Foods and Cosmetics

NO-9-12

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Background: *Caesalpinia sappan* L. (sappan heartwood) is rich in flavonoids and brazilin with recognized antioxidant potential, positioning it as a valuable natural colorant.

Objective: Study adsorption behavior of clay minerals loaded with a model natural dye and apply findings to develop sappan heartwood extract (SHE)-based colorants.

Methods: Compared adsorption of alizarin and SHE onto four clay minerals (kaolin, montmorillonite, halloysite, sepiolite) under varying ionization states/concentrations; evaluated pigmentation and photostability per ICH Q1B guidelines.

Results: All clays adsorbed alizarin best in its dianionic (neutral pH) form. DPPH assay confirmed SHE's antioxidant activity (IC50 = 3.17 ± 0.02 µg/mL). Halloysite and montmorillonite gave the strongest color intensity and stability; clay-adsorbed pigments showed much better photostability than unadsorbed extract.

Conclusion: Clay adsorption significantly improves pigment photostability, supporting sappan-clay complexes as promising stable colorants for foods, nutraceuticals, and cosmeceuticals.

Impurity Identification 1

Research on the structure-activity relationship of TCM polysaccharides based on upgraded enzymatic diagnostic purity criteria

NO-9-3

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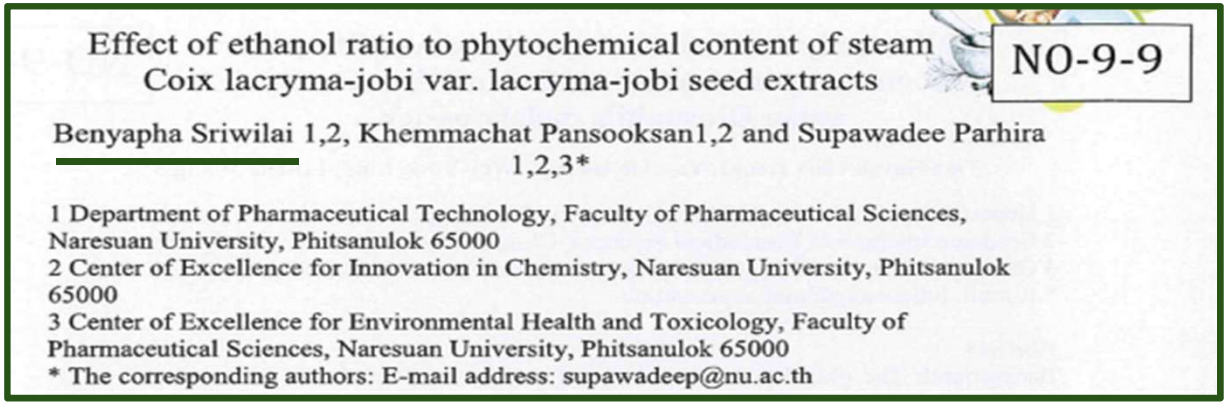
- **Background:** Commercial polygalacturonic acid (PGA), a common TCM-derived pectic polysaccharide, is often contaminated with co-purifying impurities, complicating structure-activity studies and findings reliability.
- **Objective:** Identify prevalent impurities in commercial PGA and investigate their dual role in bioactivity and hydrogel properties.
- **Methods:** Isolated impurities analyzed by MS, NMR, and methylation; immunostimulatory activity tested via RAW264.7 cells (NO, cytokines, signaling); hydrogel properties evaluated by rheology (Ca^{2+}-crosslinked gels).
- **Results:** Two impurities identified—free β-1,4-galactan and rhamnogalacturonan I with β-1,4-galactan side chains (RGI). Only RGI triggered immune responses (MAPK signaling, increased NO, IL-6, IL-1β, TNF-α); purified PGA and galactan alone were inactive. RGI removal weakened Ca^{2+}-crosslinked gels, reducing storage/loss moduli and gel microstructure.
- **Conclusion:** Co-purifying RGI, not PGA itself, drives both immunostimulatory activity and hydrogel functionality, highlighting the need for well-defined polysaccharide standards in mechanistic research and biomaterial design.

Extraction Process 1



Effect of ethanol ratio to phytochemical content of steam Coix lacryma-jobi var. lacryma-jobi seed extracts

NO-9-9

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•**Background:** Adlay (Job's tears) is a traditional medicinal grain with antioxidant/anticancer properties from phenolics and triterpenoids; extraction efficiency is strongly influenced by ethanol concentration.
•**Objective:** Evaluate the effect of ethanol polarity on phytochemical extraction using TLC profiling and quantification of total phenolic and triterpenoid content.
•**Methods:** Steamed, dried, powdered adlay seeds were extracted with 0–95% ethanol via ultrasonic-assisted extraction; extracts (CS0–CS95) were analyzed by TLC, colorimetric assay (total phenolics), and UV-Vis spectroscopy (total triterpenoids).
•**Results:** Total phenolic content increased from 0–70% ethanol (0.91–23.33 mg GAE/g) but dropped at 95% (2.73 mg GAE/g). Triterpenoid content rose steadily with ethanol concentration, peaking at 95% (288.53 mg UAE/g). Moderate ethanol (50–70%) favored phenolics, while 95% ethanol favored triterpenoids.
•**Conclusion:** Ethanol polarity critically determines phytochemical yield, with optimal extraction conditions varying by compound class—providing a basis for targeted extraction for antioxidant and anticancer applications.

New usage and/or Mechanism(s) clarification 1

Isorhamnetin has neuroprotective effects in Parkinson's Disease Models by Regulating the AKT/mTOR-TFEB Signaling Pathway

NO-9-2

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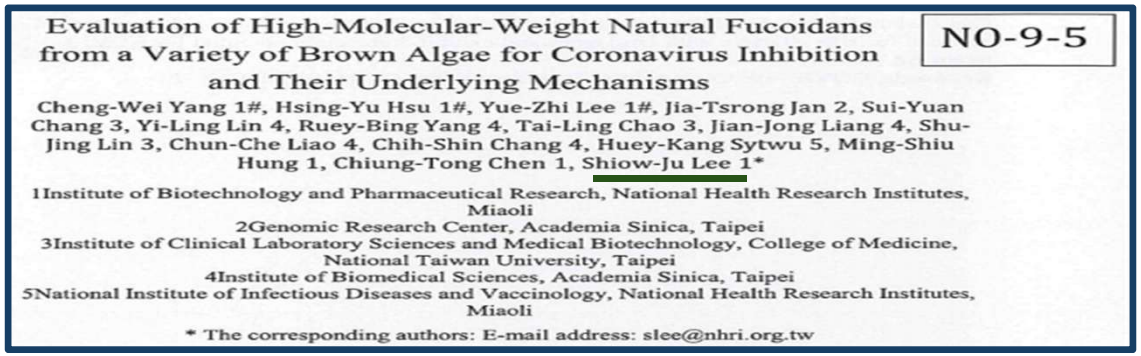
•**Background:** Parkinson's disease (PD) involves loss of nigrostriatal dopaminergic neurons and α-synuclein accumulation; Isorhamnetin has neuroprotective/anti-inflammatory activity, but its efficacy and mechanisms in PD are unclear.
•**Objective:** Evaluate Isorhamnetin's efficacy in PD, focusing on autophagy-lysosome function and neuroinflammation.
•**Methods:** Tested in an MPTP-induced mouse PD model; assessed motor function, dopaminergic integrity (TH), α-synuclein pathology, autophagy-lysosome proteomics, TFEB localization, and NLRP3 inflammasome activity (IL-1β).
•**Results:** Isorhamnetin improved MPTP-induced motor deficits, increased TH expression, and reduced pathogenic α-synuclein. It promoted TFEB nuclear translocation, activated autophagy, enhanced α-synuclein clearance, and suppressed NLRP3 inflammasome activation, lowering IL-1β.
•**Conclusion:** Isorhamnetin provides multifaceted neuroprotection by activating TFEB-mediated autophagy-lysosome pathways, clearing α-synuclein, preserving dopaminergic neurons, and reducing inflammation, supporting it as a promising candidate for PD drug development.

New usage and/or Mechanism(s) clarification 2



Evaluation of High-Molecular-Weight Natural Fucoidans from a Variety of Brown Algae for Coronavirus Inhibition and Their Underlying Mechanisms

NO-9-5

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•**Background:** High-molecular-weight fucoidans from *Undaria pinnatifida* showed potent anti-coronavirus activity, while oligo-fucoidan did not, prompting investigation of fucoidans from various brown algae and their mechanisms.

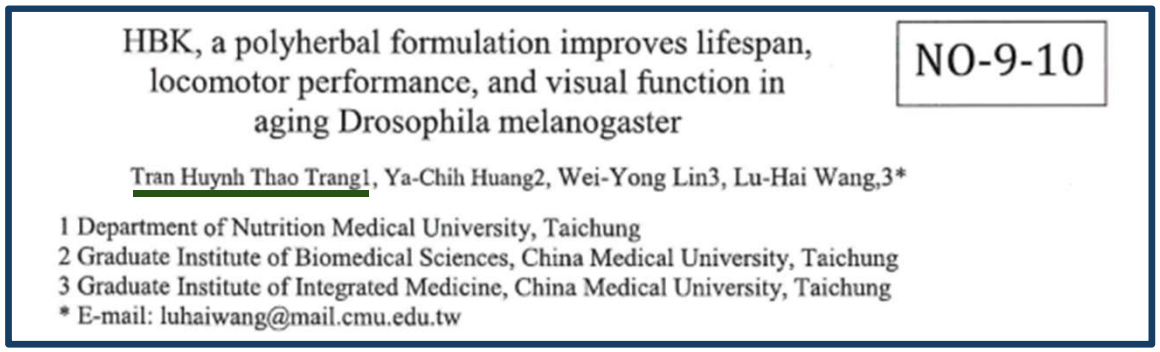
•**Objective:** Dissect the anti-coronavirus activities and underlying molecular mechanisms of naturally occurring fucoidans.

•**Methods:** Used immunofluorescence assays (HCoV-OC43, SARS-CoV-2), fucoidan-resistant HCoV-OC43 strains with spike sequence analysis, peptide competition assays, pseudovirus entry assays (furin, TMPRSS2, ACE2 binding), and in vivo testing in SARS-CoV-2-infected Syrian hamsters.

•**Results:** Four high-molecular-weight fucoidans (from *F. vesiculosus*, *F. serratus*, *L. japonica*, *U. pinnatifida*) showed potent inhibitory activity against HCoV-OC43. Resistant strain studies revealed fucoidans interfere with viral entry, potentially via interaction with host protease furin. In vivo, fucoidan treatment significantly reduced viral loads in infected hamsters.

•**Conclusion:** Fucoidans inhibit coronaviral infection by targeting the viral spike protein and host furin to block viral entry, showing therapeutic potential for COVID-19 treatment.

New usage and/or Mechanism(s) clarification 3



HBK, a polyherbal formulation improves lifespan, locomotor performance, and visual function in aging Drosophila melanogaster

NO-9-10

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•**Background:** Aging is linked to chronic low-grade inflammation (inflammaging); multi-component herbal formulations show promise as multi-target anti-aging interventions.
•**Objective:** Evaluate the anti-aging effects of HBK and its underlying mechanisms in a Drosophila melanogaster model.
•**Methods:** Male w1118 flies were administered HBK; lifespan, locomotor activity, and visual phenotypes were assessed, combined with RNA-seq and qPCR validation.
•**Results:** HBK extended lifespan by approximately 9% and improved age-related locomotor and visual decline. It modulated mitochondrial electron transport chain transcripts, suppressed inflammation-associated genes (TotA, Drosomycin, Domeless), and upregulated longevity-associated genes (Sirt6, Atg1a, Hsp70).
•**Conclusion:** HBK promotes healthy aging through modulation of mitochondrial and inflammatory signaling pathways, highlighting its potential as a multi-target nutraceutical candidate for mitigating age-related functional decline.

New usage and/or Mechanism(s) clarification 4

Novel Antipyretic Herbal Formulation Derived from Thai Traditional Medicine Scriptures via Nitric Oxide Inhibition Mechanism and Its Development as a Multiple Unit Pellet System (MUPS)

NO-9-17

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Background: Fever involves excessive pro-inflammatory mediators, particularly nitric oxide (NO); NSAIDs have limited clinical use due to side effects, making Thai Traditional Medicine (TTM) scriptures (Tak-Ka-Sila, Chan-Ta-Sart) a potential alternative source of antipyretic formulations.

Objective: Analyze antipyretic herbal formulations from TTM scriptures, characterize their phytochemistry, evaluate anti-inflammatory activity (NO inhibition), and develop/quality-control a MUPS (Multiple Unit Pellet System) dosage form.

Methods: Textual analysis identified herbal ingredients and classifications; GC-MS profiled aqueous (NDW) and ethanolic (NDE) extracts; anti-inflammatory activity assessed via NO inhibition; MUPS formulations developed and evaluated against pharmaceutical quality standards.

Results: Ten herbal ingredients with fragrant/pharmacological properties were identified; piperine was the predominant GC-MS component in NDW (33.018%), with NDE yielding 4-((2S,3R)-4-(benzo[d][1,3]dioxol-5-yl)-2,3-dimethylbutyl)-2-methoxyphenol and piperine as principal compounds. NDW showed anti-inflammatory activity (IC50 = 34.51 ± 6.17 µg/mL), comparable to acetaminophen but significantly less potent than ibuprofen. Prasachandaeng and Ha-Rak showed the most potent NO inhibitory activity (IC50 = 5.51 ± 1.79 and 6.34 ± 0.15 µg/mL). MUPS formulation Rx3 passed all quality control specifications.

Conclusion: The newly developed antipyretic formulation exhibits moderate anti-inflammatory activity consistent with its phytochemical profile, supporting further pharmacological investigation and MUPS optimization.

New usage and/or Mechanism(s) clarification 5

Usnic Acid alleviates Acute Kidney Injury by mitigating oxidative stress and inflammation via the Keap1/Nrf2 axis

NO-9-19

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Background: Acute Kidney Injury (AKI) involves tubular apoptosis, necrosis, and oxidative stress; current therapies are limited. Usnic Acid (UA), a lichen-derived compound, shows anti-inflammatory and antioxidant activity potentially acting through the Keap1/Nrf2 pathway.

Objective: Investigate UA's renoprotective effects and mechanisms in cisplatin- and ischemia/reperfusion-induced AKI, focusing on Keap1/Nrf2 signaling.

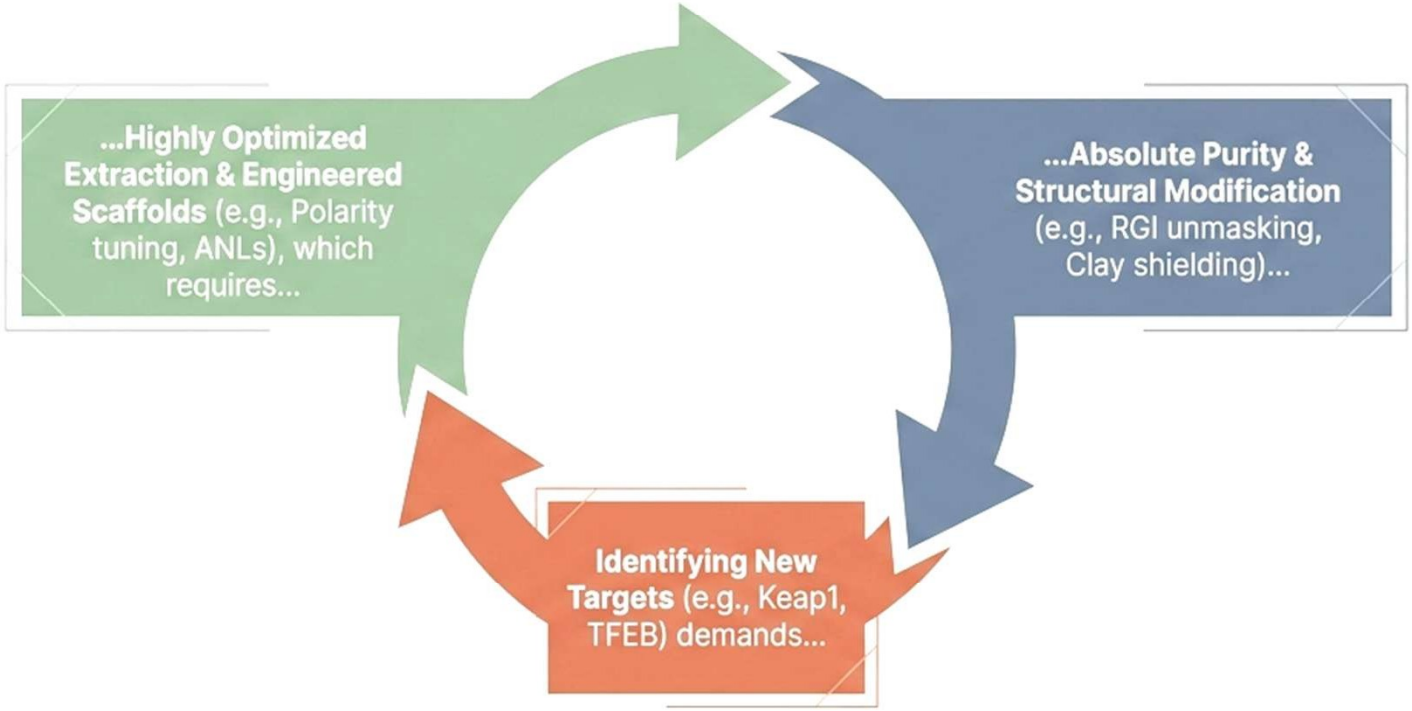
Methods: In vivo AKI models (cisplatin, renal I/R) and in vitro models (cisplatin, hypoxia/reoxygenation) in kidney tubular epithelial cells were used; RNA sequencing, molecular docking, Western blot, qPCR, and ROS/fluorescence staining assessed mechanisms.

Results: UA mitigated renal damage, inflammation, and oxidative stress in both in vivo and in vitro AKI models; it improved kidney function, reduced inflammatory responses, and inhibited oxidative stress. Mechanistic studies suggest UA activates the Nrf2 pathway through suppression of Keap1 expression.

Conclusion: UA shows promise as a therapeutic agent for cisplatin-induced renal dysfunction, exerting effects via the Keap1/Nrf2 signaling pathway.

The Natural Product Ecosystem

Session 9 did not just present isolated findings; it showcased a highly **interdependent research ecosystem** driving modern pharmacology forward.



Key Takeaway: A powerful, closing visual statement confirming that every researcher in the room is part of a unified, synergistic push toward the next generation of therapeutics.