



Multi-Target Analysis of Natural Compounds for Scar-Healing Activity

Hsi-Hsuan Shen^{1,2}, Shen-Lin Chen^{1,3}, Bo-Yan Zeng¹, Hui-Yu Tsai^{1,4}, Hsien-Tai Chiu^{1*}

¹Dept. of Chemistry, National Cheng Kung University, Tainan 701, Taiwan

²Dept. of Medicine, National Cheng Kung University, Tainan 701, Taiwan

³Dept. of Life Science, National Cheng Kung University, Tainan 701, Taiwan

⁴Dept. of Computer Science and Engineering, Texas A&M University, College Station, TX 77843, USA

*Corresponding author and Email : hchiu@mail.ncku.edu.tw



Abstract

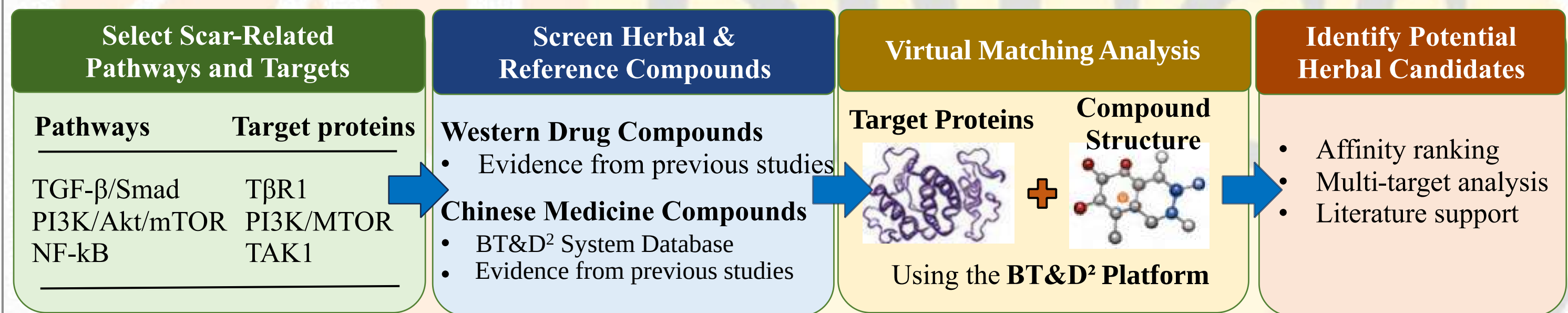
For the screening of natural compounds with scar-healing potential, in this study Taiwan BT&D² Team focused on scar formation-related TGF- β /Smad, PI3K/Akt, and NF- κ B signaling pathways and used known Western drug inhibitors as references. Virtual matching analysis was performed to evaluate the binding affinities of natural compounds from traditional Chinese medicine (TCM) to key target proteins. Natural compounds from ten TCM materials and six Western drug inhibitors were analyzed and compared based on their predicted binding affinities. The results showed that several herbal natural compounds exhibited various degree of binding affinities with multi-target binding potential, whereas known Western drug inhibitors displayed binding affinities to their designated, single targets. These findings demonstrated the potential of some TCM materials to modulate fibrosis and collagen deposition, supporting their possible development and further validation as natural candidates for scar healing applications.

Introduction

Pathological scars, including hypertrophic scars and keloids, remain a **clinical challenge** due to excessive inflammation, fibrosis, and tissue proliferation.

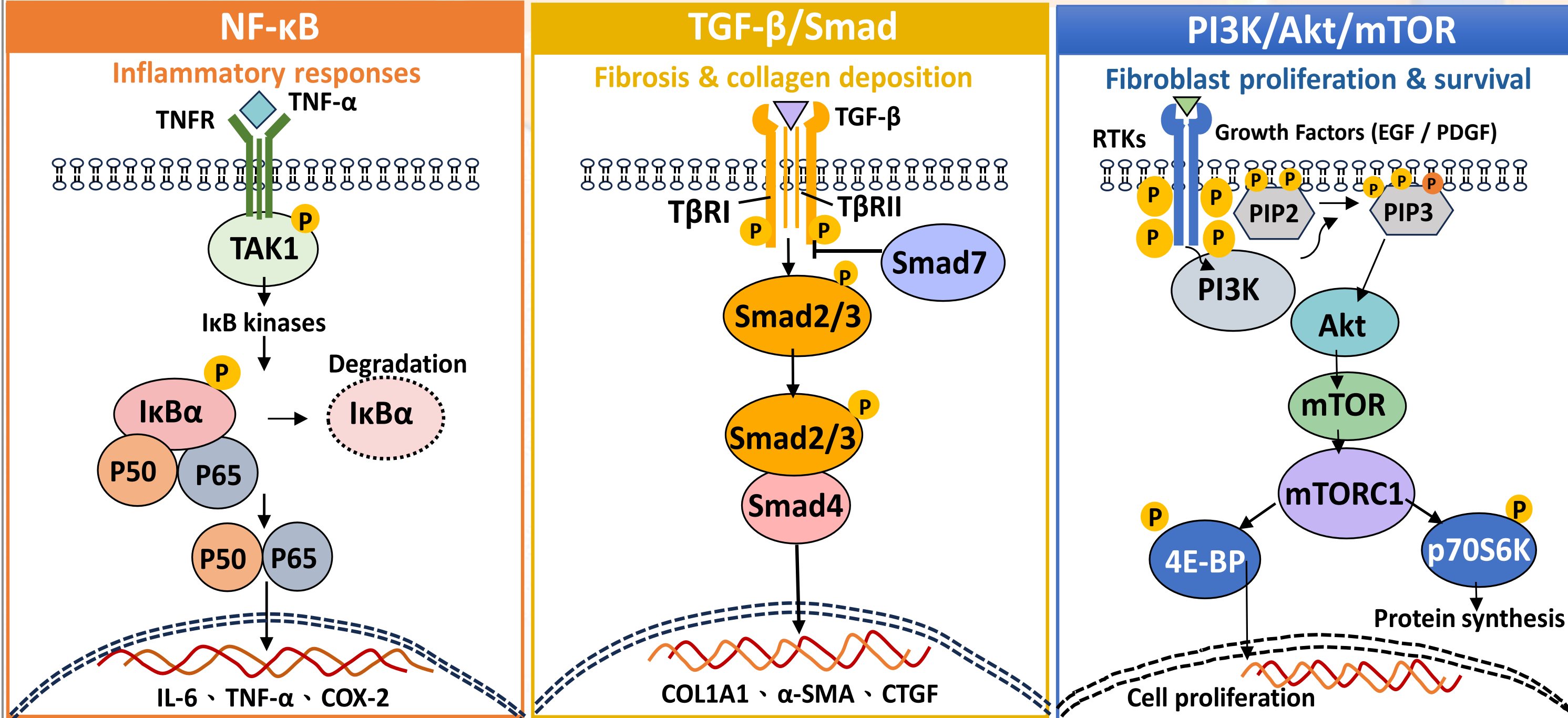
- Current treatments have **limited efficacy** and potential **adverse effects**, while **systematic multi-target** studies of natural compounds remain scarce.
- This study analyzed TCM natural compounds with potential anti-inflammatory, anti-fibrotic and anti-proliferative effects, using known Western drug inhibitors as references for comparison.

Methods



1. BT&D²-Selection of Key Scar Formation-Related Pathways and Proteins

- TGF- β /Smad, PI3K/Akt/mTOR, and NF- κ B were selected through BT&D² System for their roles in fibrosis, fibroblast proliferation, and inflammation.
- Their druggable kinase nodes, T β R1, PI3K, mTOR and TAK1, were selected as targets for analysis, with known inhibitors used as references.



2. BT&D²-Analysis of Traditional Chinese Medicine Compounds

Candidate herbs were selected from BT&D² Traditional Chinese Medicine Database based on terms related to scar healing symptoms and mechanisms.

Experimental Group [3]-[10]			
Herbal Medicine	High-Abundance Compound	Anti-Fibrotic Compound	Anti-Inflammatory Compound
Angl.	Z-lige.	Ferd.	Lige.
Bose.	Bosa.	AKB.	AKB.
Lito.	Acen.	Shin.	Shin.
Panx.	Gin1.	Not1.	Gin1.
Asta.	AstIV.	AstIV.	Forn.
Sopo.	Oxye.	Mate.	Mate.
Control Group			
Herbal Medicine	High-Abundance Compound	Anti-Fibrotic Compound	Anti-Inflammatory Compound
Ceta.	Maie.	Asid.	Maie.
Caml.	Epie.	Epie.	Epie.
Allm.	Quog.	Quen.	Quen.
Cura.	Curn.	Curn.	Curn.

In this study, the listed compounds were chosen from BT&D² TCM Database for relative abundance and anti-fibrotic/anti-inflammatory activity.

3. Selection of Western Drug Compounds

Pathway	Target Protein	Reference Inhibitor
TGF- β /Smad	T β R1	Gani. (clinical-stage) \ SB42. (research use)
PI3K/Akt/mTOR	PI3K	Apli. (approved drug)
	mTOR	Ton1. (research use)
NF- κ B	TAK1	Oxnl. \ Tanb. (both for research use)

Known small-molecule inhibitors closely associated with the target proteins were selected from primary literature and used as reference compounds for relative comparison under the same analysis conditions by BT&D² System.

4. Virtual Matching Analysis by BT&D² System

The structural information of target proteins and small molecules from Western drugs and traditional Chinese medicines were imported by and into the BT&D² system established by Taiwan BT&D² Team. Following structural processing, virtual matching was performed to analyze binding affinity of selected compounds. Candidate compounds were then analyzed for the multi-target and bioactive potential of their associated TCM materials by comparison with Western drug inhibitors.

Results

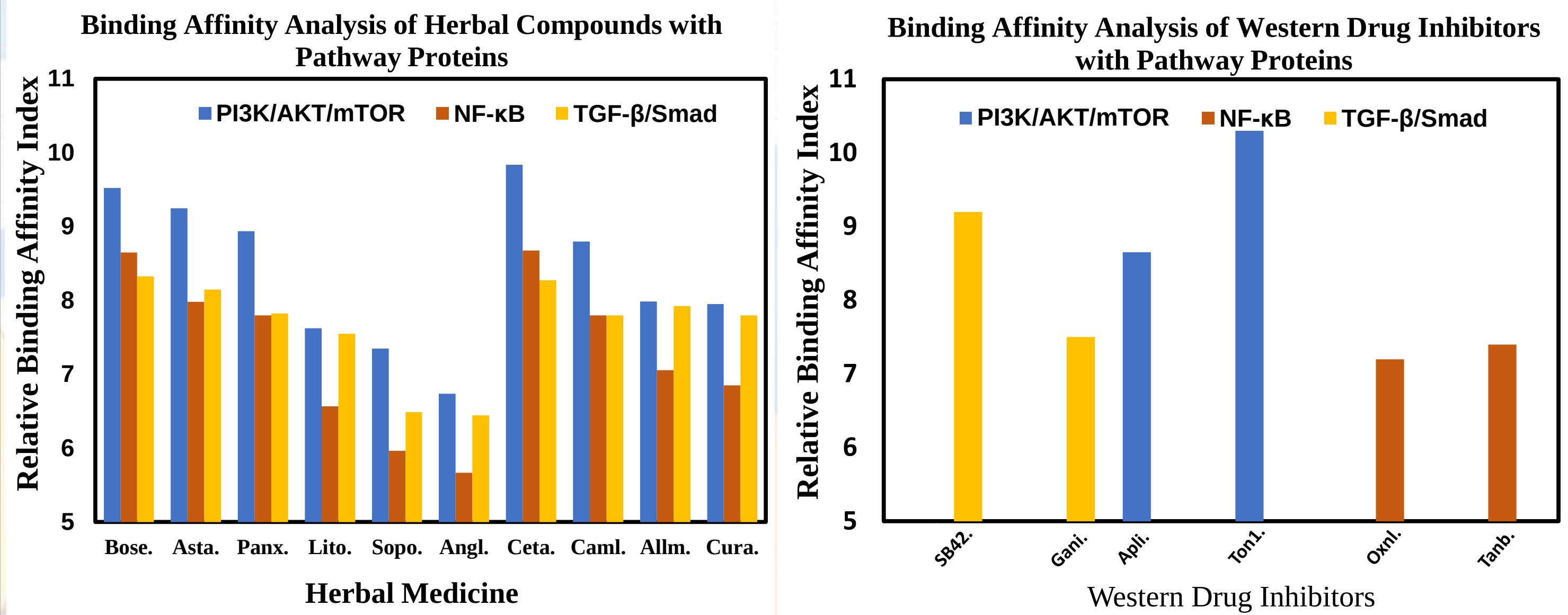


Figure 1. Relative Binding Affinities of Different Herbal Compounds Toward Pathway-Associated Proteins

Figure 2. Binding Affinity Analysis of Reference Inhibitors with Pathway Proteins

- The results showed that Bose. Asta. and Panx. were ranked as the top three candidates in binding affinity within the experimental group.
- Bose. was ranked among the top candidates across all three pathways and was therefore further compared with Ceta. and Western drug inhibitors.

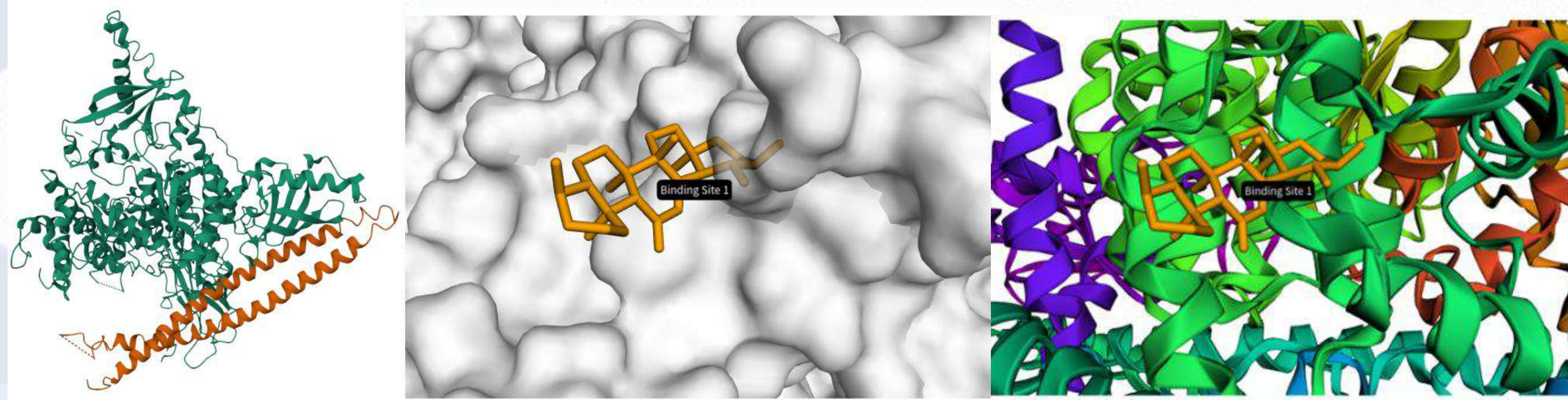
Discussion & Conclusion

1. Comparison of Binding Affinity Indices of Bose. Ceta. and Reference Inhibitors

Group	PI3K/Akt/mTOR	NF- κ B	TGF- β /Smad
Bose.	9.53	8.65	8.33
Ceta.	9.84	8.68	8.28
Reference Inhibitors	8.65-10.3	7.2-7.4	7.5-9.2
Bose. vs Reference Inhibitors	Between	Higher	Between

Across the three pathways, Bose. showed comparable binding affinity indices to those of Ceta. and similar indices to those of the reference Western drug inhibitors, suggesting its multi-pathway binding potential related to inflammation, fibrosis, and cell proliferation

2. Binding-Pose Analysis of the Top-Ranked Compound-Protein Complex



- Bosa. a bioactive compound of Bose. showed the highest Relative Binding Affinity Index (RBAI) with PI3K and was therefore selected for binding-pose analysis.
- The binding-pose analysis showed that Bosa. could occupy the active site of PI3K, suggesting its potential to inhibit PI3K function.

3. Experimental Evidence Supporting the Leading Candidate Compounds [11]-[14]

Compounds	Previous Findings	Study Model
Bose. AKB.	Modulates TGF- β /Smad signaling and inhibits NF- κ B activation and inflammatory signaling	Renal fibrosis mouse / tumor cell models
Asta. AstIV.	Modulates collagen production and reduces scar formation	Fibroblasts / rat wound model
Panx. Not.	Improves collagen organization and inhibits scar formation	Rat wound model

4. Multi-Target Regulatory Potential of Bose. Bioactive Compounds

- Cancer-target studies have reported predicted binding between Bosa. and PI3K- α .
- This study further links this **molecule-target interaction** to **fibroblast proliferation during scar formation**.
- Together with existing evidence for the effects of AKB. on TGF- β /Smad and NF- κ B signaling, Bose. may act through different bioactive compounds to target three major processes involved in scar formation: fibrosis, inflammation, and cell proliferation.

Future Direction

- Carry out Western medicine-TCM multi-target platform analysis for more natural bioactive compounds.
- Conduct further cell-based, animal, and clinical studies of Bose. and evaluate its potential for gel formulation development.
- Extend the application beyond keloids and hypertrophic scars to evaluate its potential for facial post-acne hypertrophic scars.

Reference

[1] Juan Armendariz-Borunda, et al, *Annals of Plastic Surgery*, Vol. 68, Jan.2012

[2] Elena Arribas-López, et al.,*Nutrients* 2021, 13, 2498

[3] Giuseppe Mannino, et al., *Molecules*, Vol. 21, Number 10, October 2016

[4] Minna Liu, et al., *Journal of Cellular and Molecular Medicine*, Vol. 22, Number 10, October 2018

[5] Carine Cuaz-Pérolin, et al., *Arteriosclerosis, Thrombosis, and Vascular Biology*, Vol. 28, Feb. 2008

[6] Y. Li, et al., *Frontiers in Pharmacology*, Vol. 10, 2019

[7] Hu Gao, et al., *European Journal of Dermatology*, Vol. 34, Number 5, pp. 472–479, October 2024

[8] A. El-Bakoush, et al., *Neurochemical Research*, 2018.Y. Wang, et al., *PLoS ONE*, Vol. 7, 2012

[9] M. Yang, et al., *International Immunopharmacology*, Article 115385, 2025

[10] H. Zhao, et al., *Frontiers in Pharmacology*, Vol. 8, Article 759, 2017

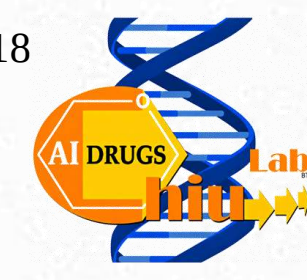
[11] Minna Liu, et al., *Journal of Cellular and Molecular Medicine*, Vol. 22, Oct. 2018

[12] Y. Takada, et al., *Journal of Immunology*, Vol. 176, pp. 3127–3140, 2006.

[13] Xi Chen, et al., *Journal of Ethnopharmacology*, Vol. 139, Feb. 2012

[14] Si-Ye Men, et al., *Journal of Cosmetic Dermatology*, Vol. 19, Feb. 2020

[15] R. Zhang, et al., *Archives of Medical Science*, Vol. 21, pp. 2522–2536, 2025.



台灣生技藥研團隊
Taiwan BT&D² Team @NCKU