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Case Report

Refractory Proctitis in a Patient with Ulcerative Colitis and Total Colectomy Alleviated by Novel Enema Therapy with Oil-Extracted *Indigo naturalis* and mesalazine: Case Report and Systems Pharmacology Analysis

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Background: Despite the availability of various novel therapeutics for treating moderate-to-severe ulcerative colitis (UC), many patients may not respond to these treatments. *Indigo naturalis* (IN) is a Chinese herbal medicine that has shown potential benefits for UC. This study aims to present the treatment course of IN enema for UC with refractory proctitis after total colectomy and to compare IN therapy with Western medicine (WM) using a systems pharmacology approach. **Material and methods:** We examined the clinical and endoscopic effectiveness of oil-extracted IN administered as enema therapy to a 67-year-old man with treatment-refractory UC from April 2021 to July 2022. The patient showed a clinical response to the IN-enema therapy. After 12 months, the patient achieved combined clinical and endoscopic remission. No adverse events directly related to IN-enema treatment were identified. One rectal bleeding episode was reported after discontinuing the IN-enema therapy. IN appeared to complement WM in treating UC, with WM affecting immunity-related pathways and IN,

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as an antioxidant, linked to inflammation and lipid-remodeling pathways. **Conclusion:** This case study suggests that oil-extracted IN enema therapy can be effective for proctitis in UC patients. A robust, randomized, controlled trial is needed to confirm the effectiveness of this therapeutic approach.

Keywords: *Indigo naturalis*, proctitis, ulcerative colitis, systems pharmacology, Enema therapy

Introduction

Ulcerative colitis (UC) is a chronic autoimmune disease of complex etiology, characterized by inflammation of the mucous membrane of the colon [1]. Despite the availability of a range of novel therapeutics for the treatment of moderate-to-severe UC, a significant proportion of patients are either primary or secondary non-responders to these agents [2]. Several studies have recently demonstrated that oral *Indigo naturalis* (IN), acting as an antioxidant, may be a therapeutic option for treating patients with UC by mouth, although some possible side effects have been reported [3,4]. Moreover, as a therapeutic option for other autoimmune diseases, topical treatment with IN has shown comparative effectiveness to immunosuppressants in the treatment of psoriasis [5].

The aim of this study was to present a treatment course with an IN enema for UC with refractory proctitis after total colectomy and to evaluate the differences between IN therapy and Western medicine (WM) using a systems pharmacology approach.

Case description

1. Treatment course with use of IN enema

We investigated the clinical and endoscopic effectiveness of oil-extracted IN administered as enema therapy to a patient with treatment-refractory UC from April 2021 to July 2022. In 2020, a 67-year-old male patient was diagnosed with UC and underwent total colectomy with rectum and anus sparing due to toxic megacolon. However, refractory proctitis became a bothersome problem despite using various therapies, including tumor necrosis factor-alpha (TNF-α) inhibitors and 5-aminosalicylic acid (5-ASA). From March 2021 to February 2022, the patient was treated with oil-extracted IN enema (twice daily) and oral mesalazine granules (2 g daily). This was followed by treatment with mesalazine-only suppositories (1 g daily) for 2 months (Figure 1). For the application of IN, we used a sterile pediatric nasogastric tube (after cutting approximately 10 cm from the tip) as a conduit through the anus. Approximately 5 cc of oil-extracted IN was administered, and then flushing was performed with approximately 10 cc of sterile normal saline. Thereafter, the patient lay flat and turned over by 90° in 15-minute intervals to ensure that the solution could touch the rectal wall as much as possible. Before the application of the IN enema, the Mayo score was 3, the Nancy histological index score was grade 4, and a large amount of blood and mucus discharge was present. In February 2022 (at the end of treatment with IN enemas and oral mesalazine), the Mayo score was 2, the Nancy histological index score was grade 1, and anal discharge had nearly disappeared (Figure 1). The

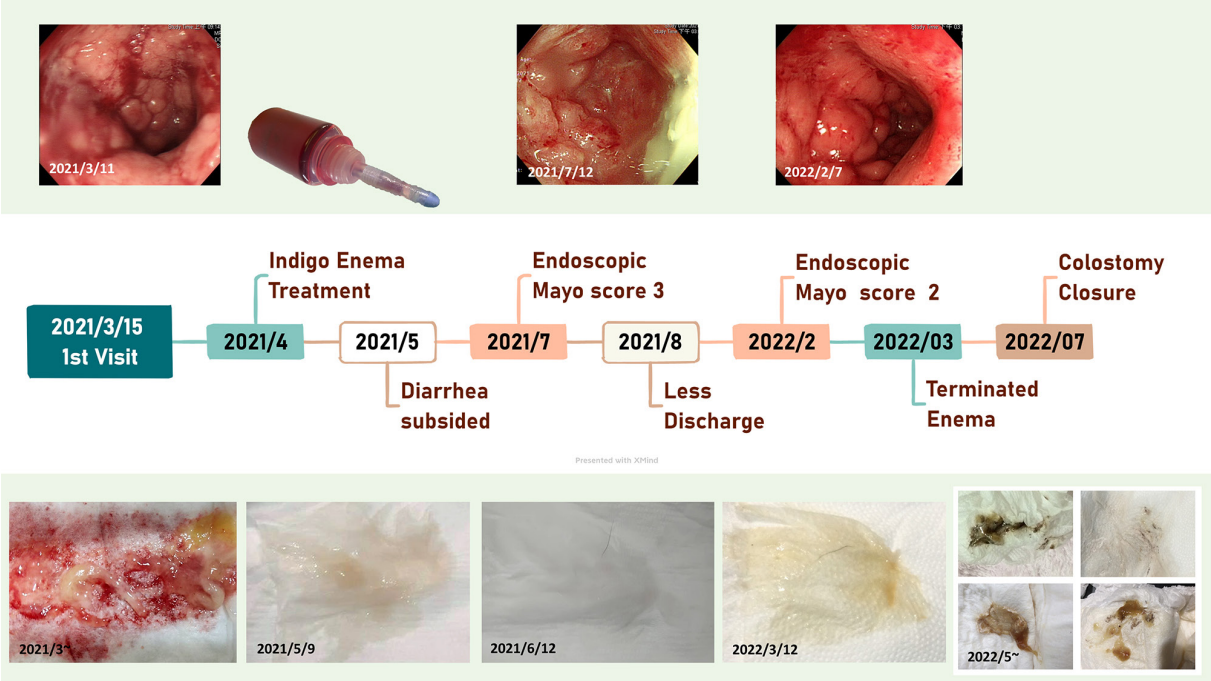

Figure 1. Representative rectal bleeding discharge, endoscopic images, and laboratory data for the patient at baseline, after treatment with *Indigo naturalis* (IN) plus oral mesalazine, and after the administration of mesalazine suppositories.

Mayo rectal bleeding subscore of the patient at baseline and at week 8 was ≥2 and 0, respectively. At 3 months after the completion of treatment with IN, the patient had worsened endoscopic Mayo scores compared with month 13, and worsened rectal bleeding was observed after the discontinuation of the IN enema.

2. Preparation of IN enema

Due to the low oral bioavailability of IN [6], we applied a novel oil extracted IN (Lindioil [7]) enema therapy for a UC patient with refractory proctitis, which indefinitely postponed the reconnection surgery between ileum and rectum. Inform consent was obtained because of the repurposing intent of using IN. The application method and clinical course were presented. The oil extracted IN was done by the traditional Chinese medicine pharmacy in the Chang Gung Memorial Hospital in Taiwan according to Lin et al.'s guide [8]. Briefly, olive oil was mixed with IN powder in a 10:1 ratio (0.5 gm IN powder in 5 cc olive oil) then being heated to 120 ℃ for 1 hour to extract the potential ingredients [8].

3. IN seems complementary to WM therapy: systems pharmacology approach

Furthermore, systems pharmacology analysis was conducted to reveal the similarities and differences between IN and WM. First, we used a target–drug interaction network to demonstrate the association between IN/WM and inflammatory bowel disease-related target proteins by consulting online biomedical databases, including the Traditional Chinese Medicine Systems Pharmacology (TCMSP), TCM Database@Taiwan, SymMap, and Search Tool for Interacting Chemicals (STITCH). The free software Cytoscape was used to present the network diagram. Second, the REACTOME database was searched for possible pharmacologic pathways underlying the

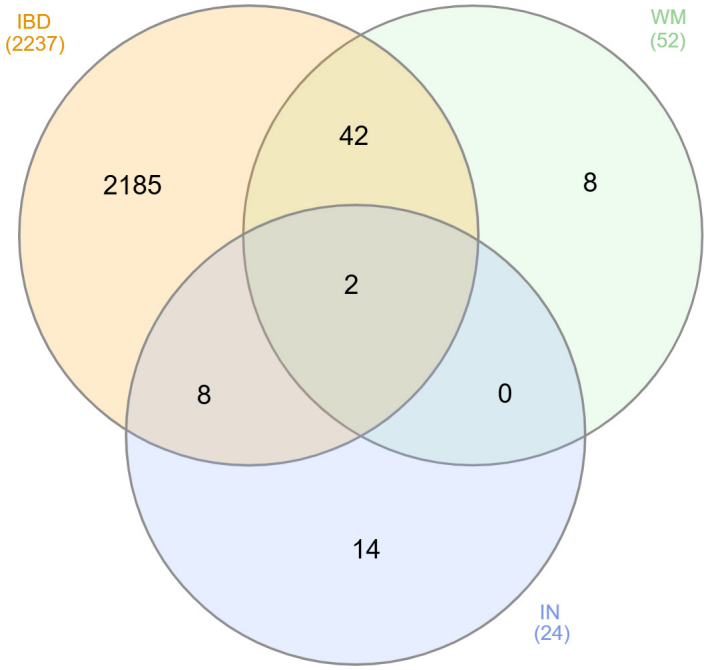

Figure 2. The IBD-related proteins covered by IN and all WM for IBD.

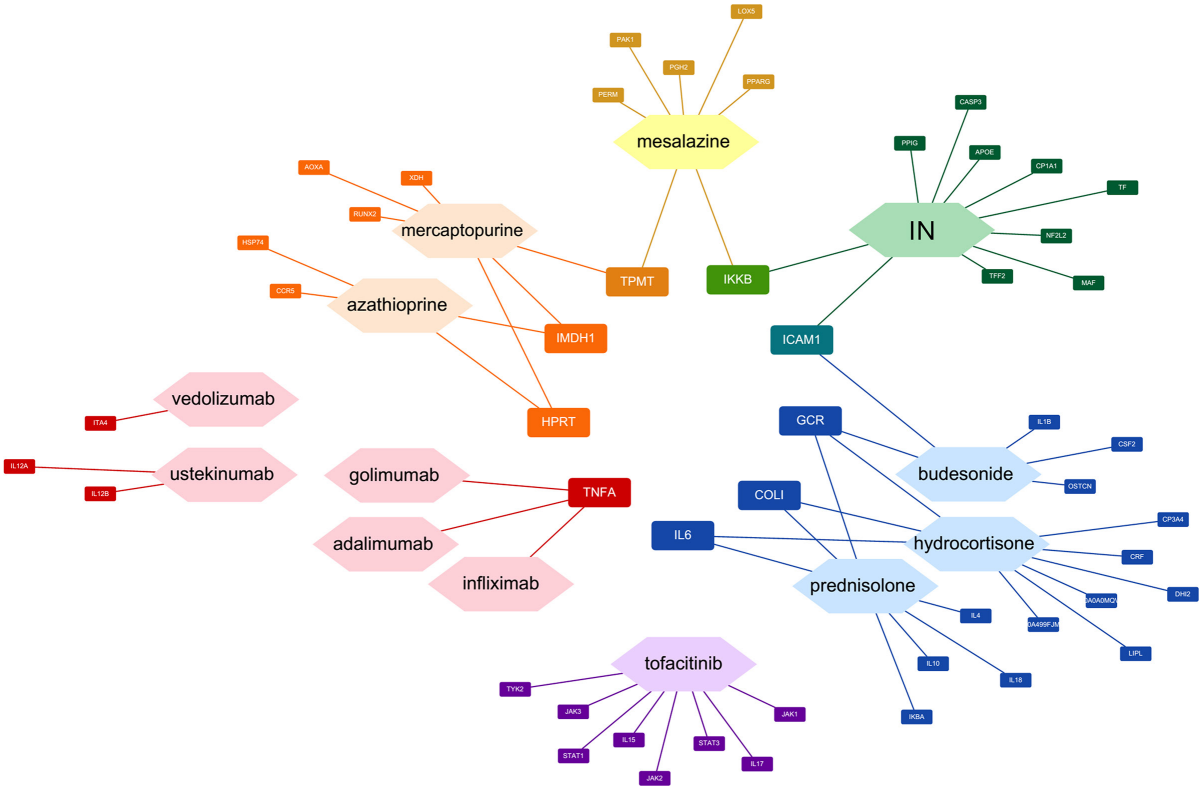

Figure 3. Protein–drug interaction network of ulcerative colitis-related proteins in relation to *Indigo naturalis* (IN) and several categories (masalazine, corticosteroids, Janus kinase inhibitor (JAKi), anti-IL12/23 p40 antibody, and TNF-α monoclonal antibody, thiopurines) of Western medicine (WM).

effects of IN on UC in comparisons with WM. The detailed data processing flow was described in our previous work [9,10].

The possible target proteins of IBD were obtained from the DisGeNet, and the IBD-related proteins are listed in the supplementary table S1 [11]. Systems pharmacology analysis demonstrated the effects of IN and WM on UC-related proteins, as well as possible pharmacologic pathways involved. IN and WM were associated with different IBD-related target proteins, and there were only two proteins targeted by both IN and WM (Figure 2). Figure 3 shows the protein-medicine network. Mesalazine and IN share an inhibitor of kappa B kinase beta (IKKB) as a target protein, and intercellular adhesion molecule 1 (ICAM1) was connected to both IN and budesonide. Peptidylprolyl isomerase G (PPIG), caspase 3 (CASP3), apolipoprotein E (APOE), cytochrome P450 1A1 (CYP1A1), transferrin (TF), nuclear factor E2-like factor 2 (NFE2L2), MAF, and trefoil factor 2 (TFF2) were linked only to IN. Collagen type I (COL1) and interleukin 6 (IL6) were targeted by corticosteroids, while hypoxanthine phosphoribosyltransferase (HPRT) and inosine monophosphate dehydrogenase 1 (IMPDH1) were related to thiopurines. In addition, Janus kinase inhibitors (JAKi), anti-IL12/23 p40 antibodies, and TNF-α monoclonal antibodies did not have mutual target proteins with IN and did not show significant interactions with any other drugs. Regarding possible pharmacologic pathways, IN appeared to play a complementary role to WM in the treatment of UC. WM involved more immunity-related pathways, while IN was linked to lipid-remodeling and transportation pathways (Figure 4 for immune system-related pathways, and Figure 5 for other IBD-related pathways).

Discussion and conclusions

We trialed a feasible treatment regimen comprising IN enema for UC proctitis and emphasized the possible complementary role of IN to WM. The results of the systems pharmacology approach could guide the choice of complementary therapy in clinical practice, and the clinical response to IN reflects the usefulness of systems pharmacology when choosing candidate treatments [12]. This is the first report of using an IN enema in this setting. The patient exhibited marked endoscopic and clinical improvement from March 2021 to February 2022, although the clinical course was altered after stopping treatment with oil-extracted IN. Enema with 5-ASA is used as a first-line therapy for proctitis. Patients with more widespread or severe UC should be treated with a combination of oral and topical 5-ASA drugs, with or without corticosteroids, to induce remission [13]. Previous studies have demonstrated the superiority of rectal treatment over oral treatment for patients with distal colitis [14]. The advent of numerous formulations of 5-ASA and corticosteroids for rectal administration, along with the substitution of traditional corticosteroids with safer agents (e.g., budesonide), has expanded the treatment options for patients with proctitis and proctosigmoiditis [15]. However, the long-term outcome of therapy with budesonide after induction treatment remains to be investigated [16]. Therefore, oil-extracted IN could be used as an alternative or complementary agent to traditional enema therapies.

In addition to its well-known antioxidant effect [4], IN significantly regulated the expression of small molecule and vesicle transportation (clearance of low-density lipoprotein, clearance and remodeling of high-density lipoprotein, and remodeling, clearance,

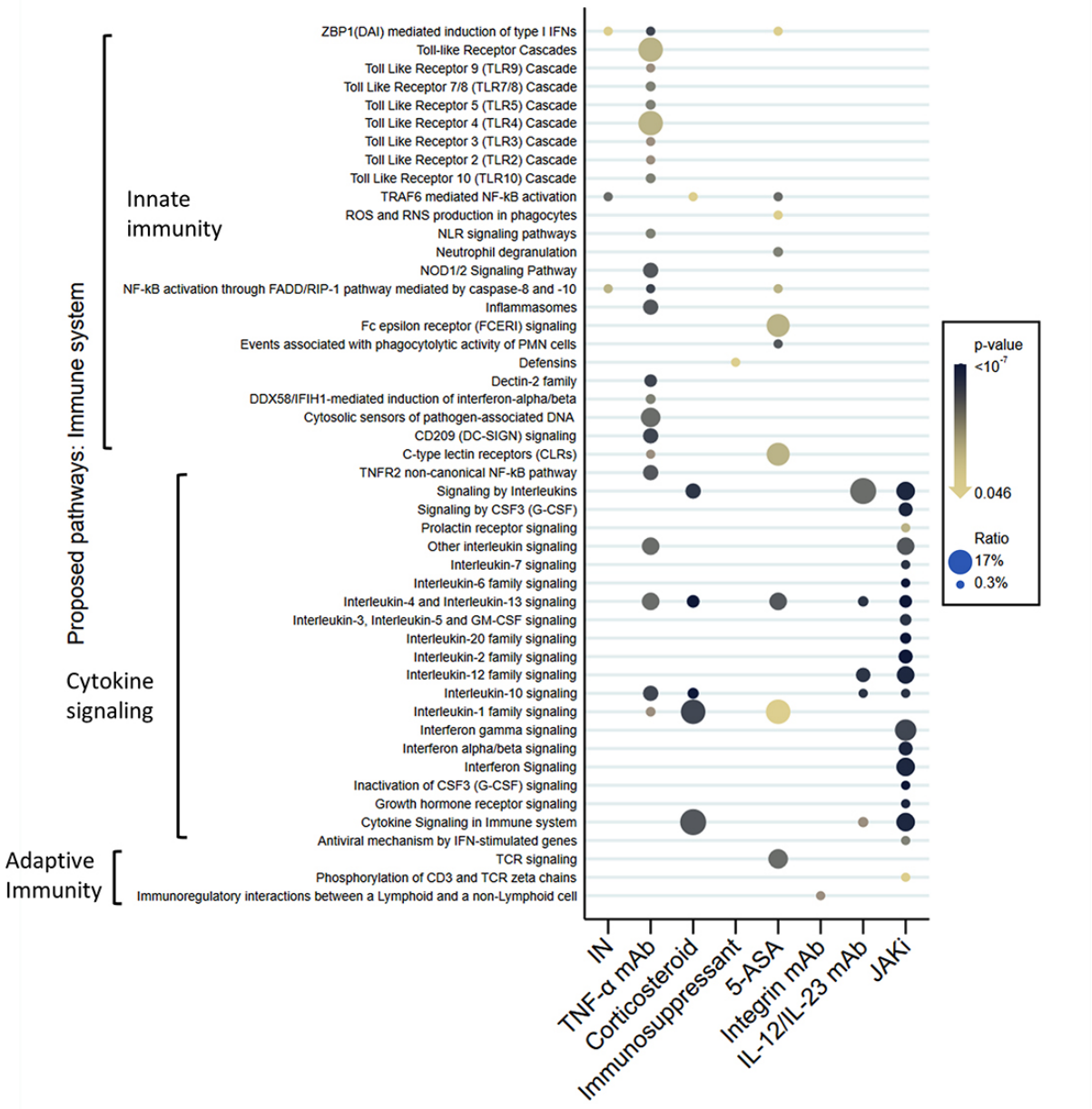

Figure 4. Differences in the proposed immune system-related molecular pathways underlying the effects of *Indigo naturalis* (IN) and WMs commonly used in IBD.

and assembly of chylomicron) according to systems pharmacology analysis results. These alterations may produce a complementary effect to that of specifically selected monoclonal antibodies. IN exerts its anti-inflammatory effects through its main active component, indirubin. This compound may regulate the TNF-α/nuclear factor-kappa B (TNF-α/NF-κB) p65 and IL6/signal transducer and activator of transcription 3 (IL6/STAT3) signaling pathways by inhibiting the degradation of IκBα and the phosphorylation of STAT3 [4]. In addition, several studies have shown that IN activates the aryl hydrocarbon receptor (AhR), which upregulates innate lymphoid cell 3 and IL22 to exert anti-inflammatory effects [17,18]. It has also been

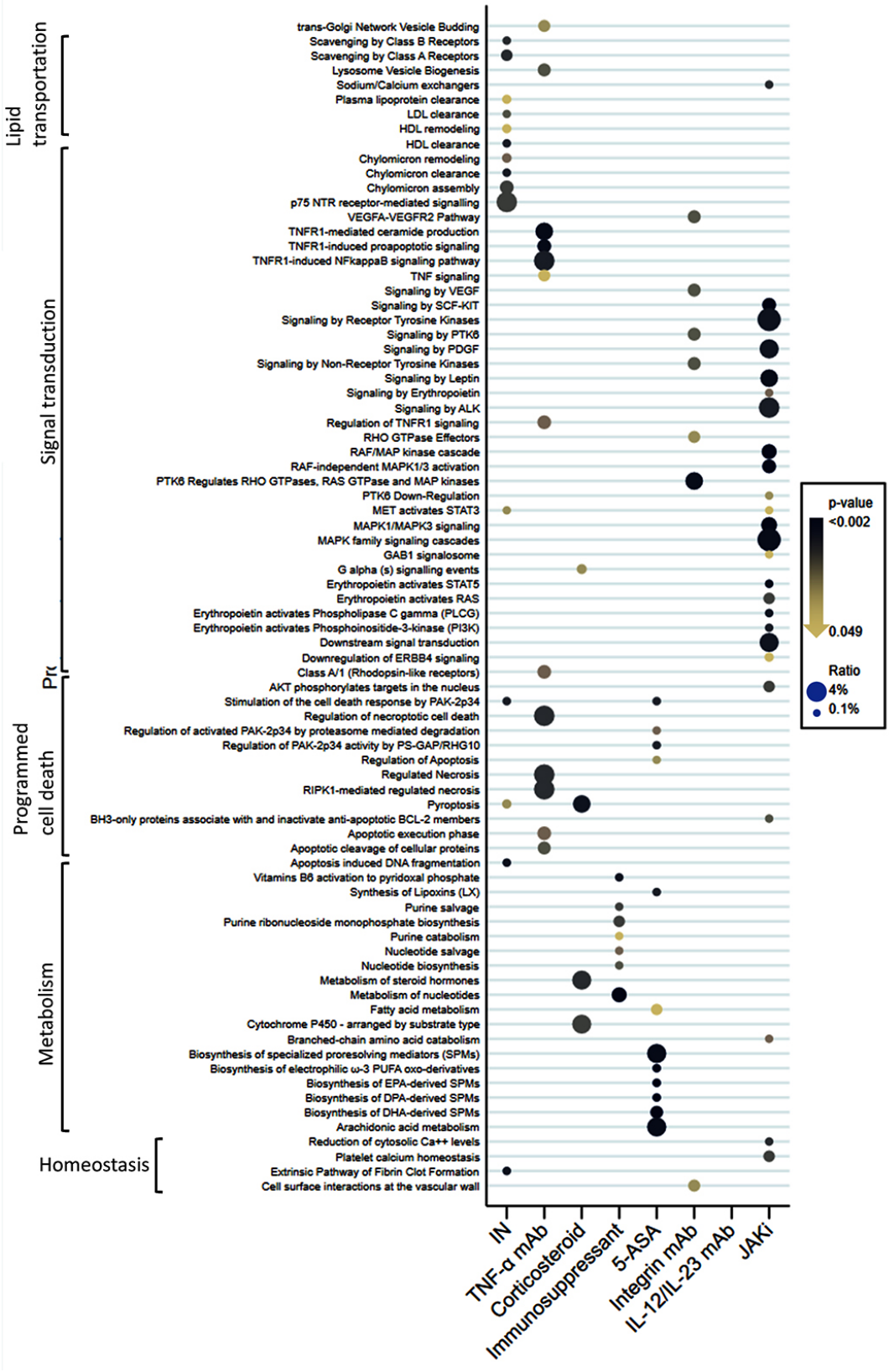

Figure 5. Differences in the proposed molecular pathways other than immune system underlying the effects of *Indigo naturalis* (IN) and WMs commonly used in IBD.

reported that AhR ligands induce anti-inflammatory effects by improving intestinal barrier permeability and reducing endotoxemia [19]. However, thus far, we are not aware of any prior studies on the clinical and endoscopic efficacy of topical IN in patients with active UC. Moreover, there is a paucity of data on the potential complementary role of topical IN with current therapeutics in patients with refractory UC. Based on a case study, we propose the use of oil-extracted IN as an enema therapy for proctitis in patients with UC. A robust, randomized, and controlled trial is warranted to validate the effectiveness of this therapeutic approach.

Abbreviations

IN, *Indigo naturalis*; UC, Ulcerative colitis; TCM, Traditional Chinese Medicine; STITCH, Search Tool for Interacting Chemicals; 5-ASA, 5-aminosalicylic acid;TNF-α, tumor necrosis factor-alpha; IKKB, kappa B kinase beta; STAT3, signal transducer and activator of transcription 3; AhR, aryl hydrocarbon receptor; ICAM1, intercellular adhesion molecule 1; PPIG, Peptidylprolyl isomerase G; CASP3, caspase 3; APOE, apolipoprotein E; CYP1A1, Cytochrome P450 1A1 (CYP1A1); TF, transferrin (TF), NFE2L2, nuclear factor E2-like factor 2; TFF2, trefoil factor 2; COL1, Collagen type I; IL6, interleukin 6; HPRT, hypoxanthine phosphoribosyltransferase; IMPDH1, inosine monophosphate dehydrogenase 1; JAKi, Janus kinase inhibitor.

Consent for publication.

Written informed consent was obtained from the patient and his family for publication of this Case report and any accompanying images.

The publication of this case report has been reviewed and approved by the Institutional Review Board (IRB) of the Chang Gung Medical Foundation. (No.: 202500470B0)

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病例報告

經油提取青黛灌腸療法緩解潰瘍性結腸炎患者經全大腸切除後之難治性直腸炎：病例報告與系統藥理學分析

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背景：儘管已有多種現有療法可用於治療中重度潰瘍性結腸炎（Ulcerative colitis, UC），但仍可能效果不彰。中藥青黛（*Indigo naturalis*, IN），對潰瘍性結腸炎顯示出潛在的益處。本研究旨在展示使用青黛萃取物灌腸療法，闡明其於潰瘍性結腸炎患者全結腸切除術後難治性直腸炎的治療過程，並透過系統藥理學方法將青黛與西藥之可能機轉進行比較。**材料與方法：**一名 67 歲潰瘍性結腸炎男性患者於全結腸切除術後出現反覆直腸炎，因西藥治療效果不佳，從 2021 年 4 月至 2022 年 7 月接受油萃取青黛灌腸療法。患者對青黛灌腸療法反應頗佳，治療 12 個月後，達到臨床與內鏡雙重緩解，且未發現與青黛灌腸治療直接相關的不良事件，然則在停用清黛灌洗後，患者曾發現一次直腸出血。青黛似乎可作為潰瘍性結腸炎之中西醫整合治療方式之一，以機轉而言，西藥主要影響免疫相關通路，而青黛作為抗氧化劑，與炎症及脂質重塑通路相關。**結論：**此個案研究表明，油萃取青黛灌腸療法對潰瘍性患者的直腸炎可能有效，但需進行嚴謹的隨機對照試驗以進一步確認此治療方法的有效性。

關鍵字：青黛 、直腸炎 、潰瘍性結腸炎 、系統藥理學 、灌腸療法

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