Reviewing not Homer’s *Iliad*, but “*Kai Bao Ben Cao*”: indigo dye—the past, present, and future

Yusuke Yoshimatsu¹, Tomohisa Sujino², Takanori Kanai¹

¹Division of Gastroenterology and Hepatology, Department of Internal Medicine and ²Center for Diagnostic and Therapeutic Endoscopy, Keio University School of Medicine, Tokyo, Japan

Heinrich Schliemann read Homer’s *Iliad* and believed in the story of Troy. He was a successful businessman in the United States, cornering the market in indigo dye. He first traveled to China and Japan in 1865 after his lucrative career in the dye business. Subsequently, he found the Troy site while visiting sites in Greece, where he established himself as a pioneer in the field of archeology 6 years after traveling through Eastern countries. If he could have read the old literature "*Kai Bao Ben Cao*" and believed in the importance of the indigo dye for ulcerative colitis (UC), he would have become a pioneer in the field of medicine. Or, in the present, we might be the second Schliemann in the field of UC.

The aryl hydrocarbon receptor (AhR) is a ligand-activated transcription factor that provides a response for toxic effects, such as dioxin. Recently, specific dietary compounds present in vegetables and metabolites digested by microbes act as the AhR ligand, and they promote intestine immune homeostasis through AhR signaling.¹⁻⁴ AhR is expressed by several kinds of immune cells,⁵⁻¹⁰ epithelial cells,¹¹ and neurons¹² in the intestine. AhR enters the nucleus by binding to its ligand and forms a heterodimer with the AhR nuclear translocator, which binds to the xenobiotic response element on DNA and triggers the transcriptional activation of target genes, such as drug-metabolizing enzymes.⁹,¹³

UC is a chronic intestinal disease, which has increased worldwide over the last few decades, especially in Asia.¹⁴,¹⁵ Western drugs, such as anti-tumor necrosis factor α and anti-IL-12/23 p40 antibody that provide systemic immunity, are currently used for UC.¹⁶⁻²² However, the old Chinese literature "*Kai Bao Ben Cao*" reported that an indigo compound was used for patients who expressed chronic blood stools around 900 AD.

Because we believed in the literature of the past like Schliemann, and Suzuki et al.²³ reported the retrospective study about the efficacy of indigo naturalis (IN), which mainly contains AhR ligands, on patients with UC in Japan, we conducted prospective clinical trial of IN for them,²⁴ followed by a randomized controlled trial (INDIGO study).²⁵ As a result, we demonstrated that 8 weeks of IN is safe and effective in patients with UC, even if in treatment refractory patients.²⁵,²⁶ Recent Western technologies revealed that AhR ligands lead to innovative treatments that promote the regeneration of mucosal epithelial cells.²⁷,²⁸ Of note, IN causes adverse effects, such as headaches, gastrointestinal symptoms, mild liver dysfunction, non-specific enteritis, bowel intussusception, and pulmonary arterial hypertension.²⁹⁻³¹ As a consequence, inspired by the anti-colitic effect of the AhR ligand, both clinical and basic research studies on the efficacy and safety of IN are being conducted.²⁴,³²⁻³⁴ Based on these verifications, we are preparing a consensus statement on the appropriate use of IN based on the fact-finding survey, while developing indigo containing capsule that disintegrates in the large intestine for the clinical trial (first in human) in order to reduce side effects because indigo is extracted as the active ingredient of IN³¹ and is assumed to be

© Copyright 2022. Korean Association for the Study of Intestinal Diseases.
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.
absorbed in the small intestine due to its insolubility. Safe AhR ligand-based drugs will become a novel treatment strategy for inflammatory bowel diseases in the near future. Although the precise mechanism is still unknown, new technology will illuminate the truth in the ancient documents.

### ADDITIONAL INFORMATION

#### Funding Source
The authors received no financial support for the research, authorship, and/or publication of this article.

#### Conflict of Interest
No potential conflict of interest relevant to this article was reported.

#### Data Availability Statement
Not applicable.

#### Author Contribution
Conceptualization: all authors. Project administration: Kanai T. Resources: all authors. Software: Yoshimatsu Y. Supervision: Sujino T. Validation: Kanai T. Writing original draft: Yoshimatsu Y. Writing review & editing: Sujino T, Kanai T. Approval of final manuscript: all authors.

#### ORCID
Yoshimatsu Y https://orcid.org/0000-0002-7282-870X
Sujino T https://orcid.org/0000-0003-0699-6577
Kanai T https://orcid.org/0000-0002-1466-4532

#### REFERENCES


