Pharmabiotics, *Phocaeicola dorei*, ameliorates liver fibrosis by alleviating macrophage efferocytosis of neutrophils

Ki Tae Suk[1], Jung A Eom[1], In-Gyu Park[1], Sang Jun Yoon[1], Goo Hyun Kwon[1], Young Lim Ham[2], Dong Joon Kim[1]

1 Institute for Liver and Digestive Diseases, Hallym University, Chuncheon, Republic of Korea

2 Daewon University College, Department of Nursing, Jaecheon, Republic of Korea

INTRODUCTION

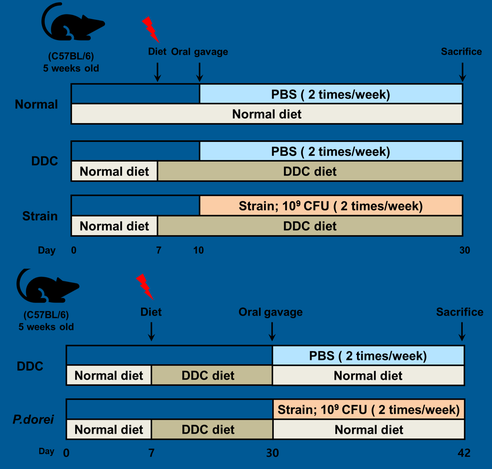
Liver fibrosis results from chronic inflammation, dysregulated immune responses, and persistent activation of hepatic stellate cells (HSCs). Increasing evidence shows that gut microbiota influences hepatic immunity and fibrogenesis. *Phocaeicola dorei* has been reported to ameliorate metabolic diseases. Its role in liver fibrosis remains unclear.

AIM

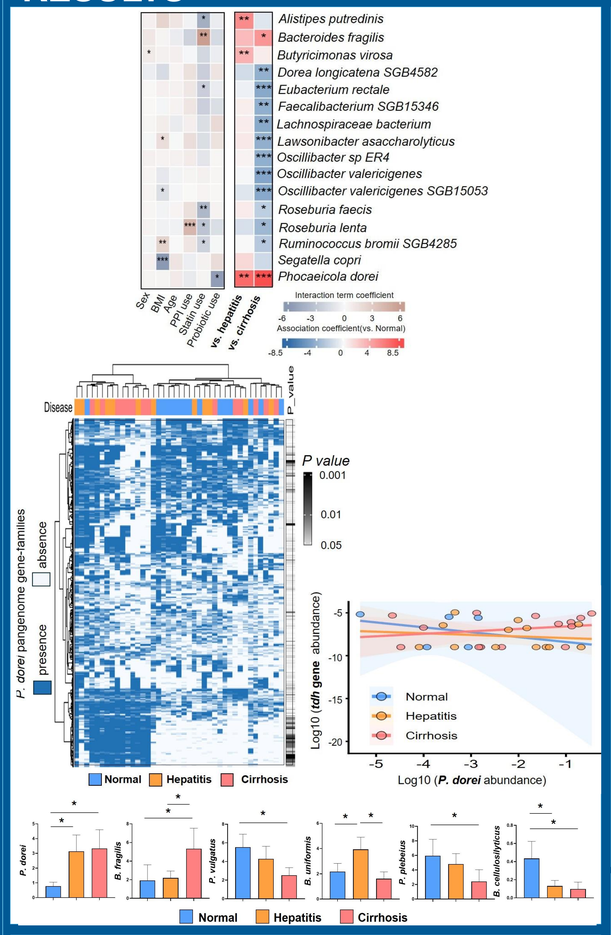
We hypothesized that *P. dorei* attenuates liver fibrosis by suppressing neutrophil activation and limiting macrophage-mediated efferocytosis of apoptotic neutrophils, thereby reducing downstream HSC activation.

METHOD

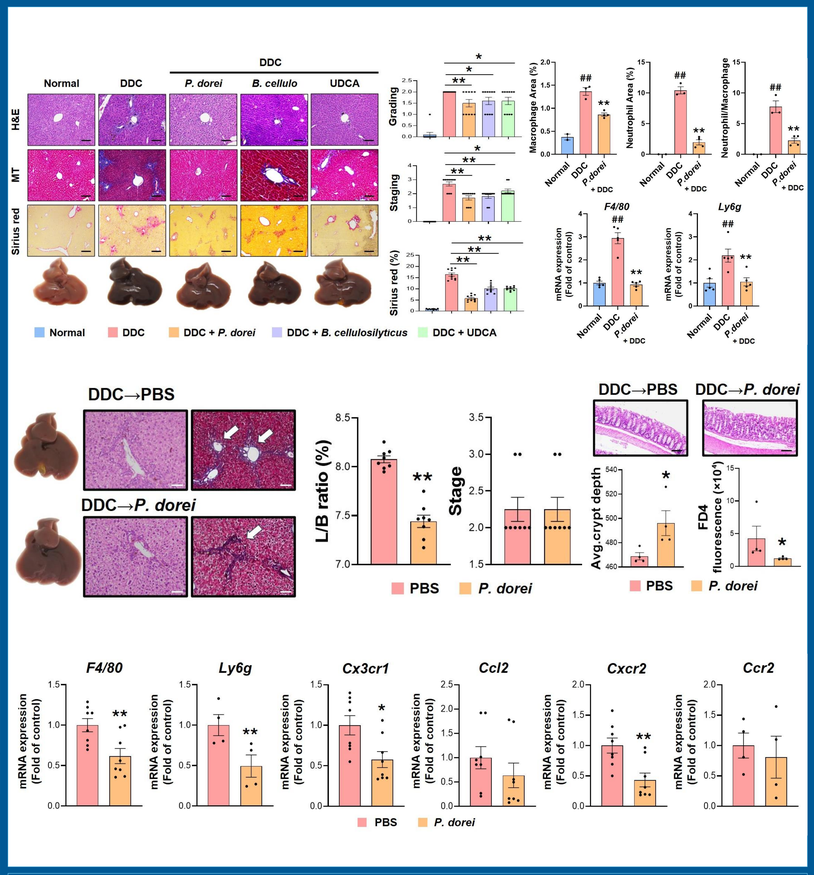
- Fecal samples were collected from healthy controls and patients (n=285) to assess the clinical relevance of *P. dorei*.
- In mice model, 3,5-diethoxycarbonyl-1.4-dihydrocollidine (DDC) diet and *P. dorei* (10^9 CFU/g twice/week) was orally administered.
- Fibrosis severity, collagen deposition, immune-cell infiltration, and chemokine expression were assessed by histology, Sirius Red staining, immunofluorescence, and qPCR.
- HSCs were isolated for RNA sequencing to identify pathway changes modulated by *P. dorei*.
- Primary HSCs, LX-2, THP-1, and HL-60 cell lines were used for mechanical validation.



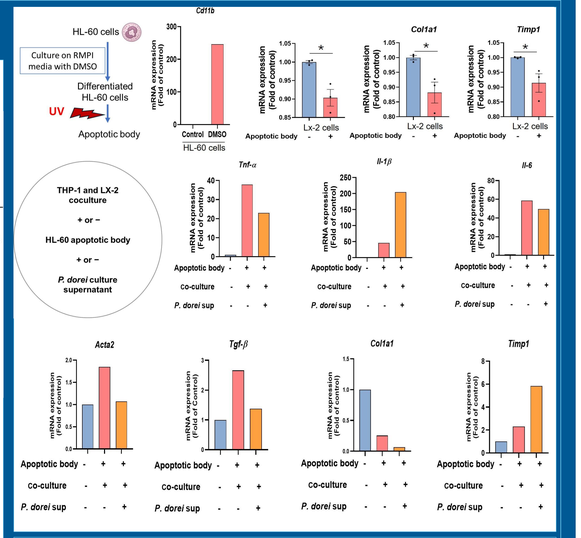
RESULTS



The relative abundance of *P. dorei* increased progressively with worsing liver disease in human cohort.



P. dorei administration significantly reduced neutrophil degranulation and efferocytosis pathways, as indicated by decreased *Ly6g* and *F4/80* expression.
In parallel, the dysregulated expression of neutrophil-associated chemokines, including *Cx3cl1*, and *Cx3cr1* was restored by *P. dorei* treatment.



In vitro, *P. dorei* culture supernatant markedly inhibited macrophage-mediated efferocytosis.

	Top20 compounds	P-value	Fold change
Upregulated compounds	Prolylleucine	8.35E-05	191.6646
	Proline	0.000532	33.01727
	Leucylproline	0.000845	12.44538
	Arginine	0.000456	7.142543
	Valylproline	0.010624	7.028631
	L-Alanyl-L-proline	0.000366	4.872177
	Pipecolinic acid	6.43E-06	3.094503
	Adenine	1.38E-05	2.771951
	Indole-3-acrylic acid	2.49E-05	2.762606
	6-Methylquinoline	9.14E-05	2.736851
Downregulated compounds	Glycoursodeoxycholic acid	0.0000102	1119.821
	Glycocholic acid	0.000083	1106.195
	Taurocholic acid	0.00000398	812.3477
	Deoxycholic acid	0.0001	312.0125
	Taurochenodeoxycholic acid	0.0000146	149.8127
	Cholic acid	0.0000771	79.44705
	Adenosine	0.0000112	43.80393
	Inosine	0.00021	26.87377
	Carnosine	0.000000443	19.97563
	Hypoxanthine	0.00033	12.31709

Metabolic comparison between RCM control and cell-free supernatant of *P. dorei.*

CONCLUSIONS

Collectively, *P. dorei* attenuates liver fibrosis by suppressing neutrophil and macrophage infiltration and disrupting efferocytosis through interference with interactions between apoptotic bodies and macrophages. Our results identify *P. dorei* as a potential microbiome-based therapeutic candidate for liver fibrosis.

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CONTACT INFORMATION

Ki Tae Suk, M.D., Ph.D (ktsuk@hallym.ac.kr)