可能性が示唆された（Fig.5）。

３．LEMの抗HCV活性の評価

（１）LEMのHCV侵入阻害活性評価

H77株（遺伝子型1a）およびCon1株（遺伝子型1b）のHCVpvを用いて、LEMのHCV侵入阻害活性を検討した。その結果、LEMの添加濃度依存的にHCVpvの侵入による細胞内ルシフェラーゼ活性の上昇が抑制されており、LEMがHCVpvの細胞内侵入を抑制していることが示唆された（Fig.6 A,C）。またこの時、細胞障害性の評価を行ったところ、LEMにより細胞が障害されている様子は観察されなかった（Fig.6 B,D）。

（２）LEMのHCV複製阻害活性評価

HCVレプリコン細胞を用いて、LEMのHCV複製阻害活性を検討した。その結果、LEMの添加濃度依存的に細胞内ルシフェラーゼ活性の低下、および細胞内HCV RNAの量が低下している様子が観察され、LEMがHCV複製阻害活性を有していることが示唆された（Fig.7 A,C）。この時、細胞障害性の評価を行ったが、LEMにより細胞が障害されている様子は観察されなかった（Fig.7 B）。

４．低分子化リグニンのHCV侵入阻害活性評価

HCVpvを用いて、低分子化リグニンのHCV侵入阻害活性を検討した。その結果、低分子化リグニンの添加濃度依存的にHCVpvの侵入による細胞内ルシフェラーゼ活性の上昇が抑制されており、低分子化リグニンがHCVpvの細胞内侵入を抑制していることが示唆された（Fig.8 A,C）。またこの時、細胞障害性の評価を行ったところ、低分子化リグニンにより細胞が障害されている様子は観察されなかった（Fig.8 B,D）。さらに、細胞培養系により作製されたHCV粒子（HCVcc）を用いて、低分子化リグニンのHCV侵入阻害活性を検討した。その結果、低分子化リグニンの添加濃度依存的にHCVccの侵入による細胞内HCV RNA量の上昇が抑制されており、低分子化リグニンがHCVccの細胞内侵入を抑制していることが示唆された。以上のことから、低分子化リグニンがHCV侵入阻害活性を有していることが明らかとなった（Fig.9）。

D. 考察

iPS細胞からiPS-hep細胞に至るまでの各分化段階の細胞における遺伝子発現をアレイ解析することで、HCV侵入について９９遺伝子、HCV複製について３３遺伝子の必須遺伝子候補が絞り込まれた。今回候補として挙げられた遺伝子群の中には、HCV侵入ではCES1やAADAC、HRGが、HCV複製ではHMGCSやASGRといった遺伝子が既にHCV侵入、あるいはHCV複製に関与する遺伝子であるとの報告がなされており、候補として挙げられた遺伝子とHCV侵入およびHCV複製との関係を検証することで、あらたなHCV治療薬の創薬ターゲットとなり得るのではないかと考えている。今後、得られた候補遺伝子についてHCV侵入および複製との関与の有無について解析を進める予定である。

また、今回新たに抗HCV薬候補物質としてLEM、および低分子化リグニンについて解析を行い、LEMおよび低分子化リグニンに抗HCV活性が認められた。リグニンは植物においてセルロースに次いで含量の多い成分であり、その製造は比較的安価に行うことが可能と考えられる。また、LEMおよび低分子化リグニンでは肝保護作用と抗HCV作用の２つの側面からC型肝炎に対し

て効果を発揮する可能性が考えられる。今後、LEM および低分子化リグニンが、HCV と同じく肝臓を宿主臓器とする HBV に対して抗 HBV 効果を発揮しうるか検討を行う予定である。

E. 結論

大阪大学大学院薬学研究科　水口グループによって確立されたヒト iPS 細胞由来肝細胞分化誘導系を用いて HCV 侵入および複製に関与する候補遺伝子の絞り込みを行い、HCV 侵入について９９遺伝子、HCV 複製について３３遺伝子の候補を得た。これら候補遺伝子から、HCV 侵入および複製に必須の新規宿主因子を同定することができれば、新たな HCV 治療薬の創薬ターゲットとなることが期待される。

また、LEM および低分子化リグニンの HCV に対する効果を検討し、LEM および低分子化リグニンが肝保護作用および HCV 侵入阻害作用を有していることを明らかとした。また、LEM には HCV 複製阻害活性が認められることを明らかとした。今後 LEM および低分子化リグニンの抗 HCV 活性について詳細に検討することで、より安価な HCV 治療薬の開発につながることが期待される。

F. 研究発表

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第 134 回日本薬学会（2014）、３月２７日～３０日、熊本

G. 知的所得権の出願・登録状況

1. 特許取得

2. 実用新案登録

3. その他

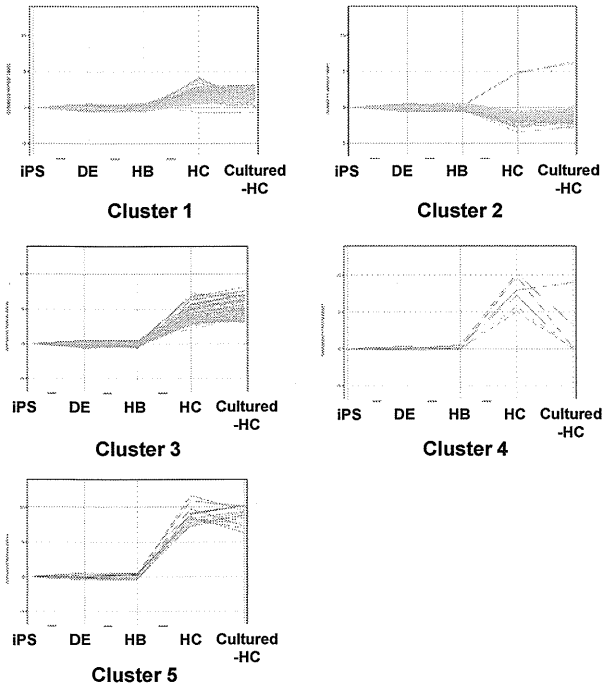

Fig.1 Hierarchical clustering analysis of iPS cells and iPS-derived definitive endoderm (DE), hepatoblast (HB), hepatocytes (just after differentiation or cultured; HC and cultured HC) for identification of HCV entry related genes. Cluster 1, 3, 5 include genes which expression increases slightly (cluster 1), moderately (cluster 3), or greatly (cluster 5) in HC compared with HB, and keep up in cultured HC. Cluster 2 includes genes which expression decreases in HC compared with HB. Cluster 4 includes genes which expression increases in HC compared with HB, but decreased in cultured HC compared with HC.

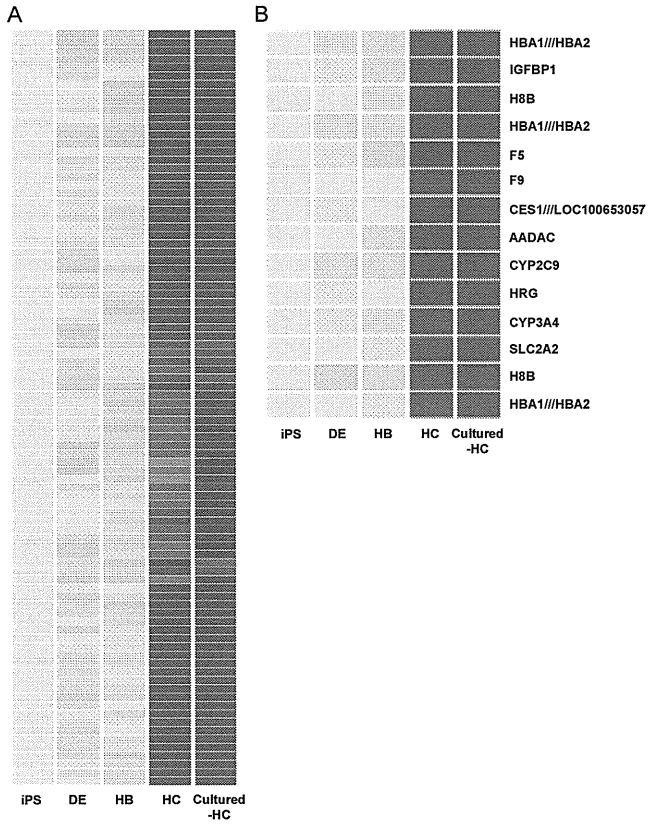

Fig.2 Heat maps showing cluster 3 (A) and 5 (B) in Fig.1. Yellow shows low expression, and red shows high expression. Gene names in cluster 3 or 5 are shown in right column (B) and table 1.

Gene Symbol	Gene name
GATM	glycine amidinotransferase (L-arginine:glycine amidinotransferase)
PLEK	pleckstrin
CCL4	chemokine (C-C motif) ligand 4
UGT1A1///UGT1A10///UGT1A4 ///UGT1A6///UGT1A8///UGT1A9	UDP glucuronosyltransferase 1 family, polypeptide A10
ATF5	UDP glucuronosyltransferase
FGL1	fibrinogen-like 1
HSD11B1	hydroxysteroid (11-beta) dehydrogenase 1
DNASE1L3	DNASE1L3
F12	coagulation factor XII (Hageman factor)
CYP3A7	cytochrome P450, family 3, subfamily A, polypeptide 7
SLC38A3	solute carrier family 38, member 3
PLA2G5	phospholipase A2, group V
NR1H4	nuclear receptor subfamily 1, group H, member 4
PON1	paraoxonase 1
XPNPEP2	X-prolyl aminopeptidase (aminopeptidase P) 2, membrane-bound
APOC2///APOC4///APOC4-APOC2	apolipoprotein
ASGR1	asialoglycoprotein receptor 1
NAT2	N-acetyltransferase 2 (arylamine N-acetyltransferase)
CFHR2	complement factor H-related 2
AGXT	alanine-glyoxylate aminotransferase
UGT1A1///UGT1A10///UGT1A4 ///UGT1A6///UGT1A8///UGT1A9	UDP glucuronosyltransferase 1 family, polypeptide A10
CYP2A6	cytochrome P450, family 2, subfamily A, polypeptide 6
IL1RL1	interleukin 1 receptor-like 1
CYP1A2	cytochrome P450, family 1, subfamily A, polypeptide 2
BLNK	B-cell linker
ABCB4	ATP-binding cassette, sub-family B (MDR/TAP), member 1 /// ATP-binding cassette, sub-family B (MDR/TAP), member 4
C4A///C4B///LOC100293534	complement component 4A (Rodgers blood group) /// complement component 4B (Childo blood group)
AZGP1	alpha-2-glycoprotein 1, zinc-binding
FBP1	fructose-1,6-bisphosphatase 1
ABCB1///ABCB4	ATP-binding cassette, sub-family B (MDR/TAP), member 1
C6	complement component 6
CCL14///CCL14-CCL15///CCL15	chemokine (C-C motif) ligand 14 /// chemokine (C-C motif) ligand 15
CYP4F2///CYP4F3	
LBP	lipopolysaccharide binding protein
AKR1C2///LOC100653286	aldo-keto reductase family 1, member C2 (dihydrodiol dehydrogenase 2; bile acid binding protein; 3-alpha hydroxysteroid dehydrogenase, type III)
PTGDS	prostaglandin D2 synthase 21kDa (brain)
HLA-DQA1///HLA-DQA2 ///LOC100507718///LOC100509457	
COL14A1	collagen, type XIV, alpha 1
DPT	dermatopontin
LAMA2	laminin, alpha 2 (merosin, congenital muscular dystrophy)
APOC1	apolipoprotein C-I
NKG7	natural killer cell group 7 sequence
ADH6	alcohol dehydrogenase 6 (class V)
PLGLA///PLGLB1///PLGLB2	plasminogen-like B2 /// plasminogen-like B1
CYP2C9	cytochrome P450, family 2, subfamily C, polypeptide 9
SPP2	secreted phosphoprotein 2, 24kDa
IGK@///IGKC///LOC100294406	IGK@ /// IGKC
PLA2G5	phospholipase A2, group V
CYP2C9	
CYP2C19	cytochrome P450, family 2, subfamily C, polypeptide 19
IGK@///IGKC	IGK@ /// IGKC
LAMA2	laminin, alpha 2 (merosin, congenital muscular dystrophy)
AZGP1///AZGP1P1	alpha-2-glycoprotein 1, zinc-binding
HBB	Hemoglobin, beta
SQRDL	sulfide quinone reductase-like (yeast)
TMEM140	transmembrane protein 140
GIMAP4	GTPase, IMAP family member 4
COLEC11	collectin sub-family member 11
GBA3	glucosidase, beta, acid 3 (cytosolic)
SLC22A7	solute carrier family 22 (organic anion transporter), member 7
SLC38A4	solute carrier family 38, member 4
FGF21	fibroblast growth factor 21
RBP4	Retinol binding protein 4, plasma
ADH4	alcohol dehydrogenase 4 (class II), pi polypeptide
ANGPTL1	angiopoietin-like 1
IGK@///IGKC///LOC100294406	immunoglobulin kappa constant /// immunoglobulin kappa locus
LOC389834///MAFIP///TEKT4P2	hypothetical gene supported by AK123403
UPB1	ureidopropionase, beta
HFE2	hemochromatosis type 2 (juvenile)
GOLT1A	golgi transport 1 homolog A (S. cerevisiae)
A1BG	alpha-1-B glycoprotein
APOH	apolipoprotein H (beta-2-glycoprotein I)
CYP8B1	cytochrome P450, family 8, subfamily B, polypeptide 1
LOC149703	hypothetical protein LOC149703
SLC25A47	
HEPACAM///HEPN1	hepatocyte cell adhesion molecule
XDH	xanthine dehydrogenase
DCN	Decorin
IL1RL1	interleukin 1 receptor-like 1
RTP3	receptor (chemosensory) transporter protein 3
CFHR3	Complement factor H-related 3
CYP4A11	cytochrome P450, family 4, subfamily A, polypeptide 11
TAT	tyrosine aminotransferase
AKR1C1///AKR1C2 ///LOC100653286	aldo-keto reductase family 1, member C1 (dihydrodiol dehydrogenase 1; 20-alpha (3-alpha)-hydroxysteroid dehydrogenase)
HEATR7B1	
LOC100507389	
LOC100507389	
LOC201651	similar to Arylacetamide deacetylase (AADAC)

Table 1 Gene names in cluster 3

Gene symbol	Gene name
HBA1 /// HBA2	hemoglobin, alpha 1 /// hemoglobin, alpha 2
IGFBP1	Insulin-like growth factor binding protein 1
HBB	Hemoglobin, beta
F5	coagulation factor V
F9	coagulation factor IX
CES1	carboxylesterase 1
AADAC	arylacetamide deacetylase (esterase)
CYP2C9	cytochrome P450, family 2, subfamily C, polypeptide 9
HRG	histidine-rich glycoprotein
CYP3A4	cytochrome P450, family 3, subfamily A, polypeptide 4
SLC2A2	solute carrier family 2 (facilitated glucose transporter), member 2

Table 2 Gene names in cluster 5

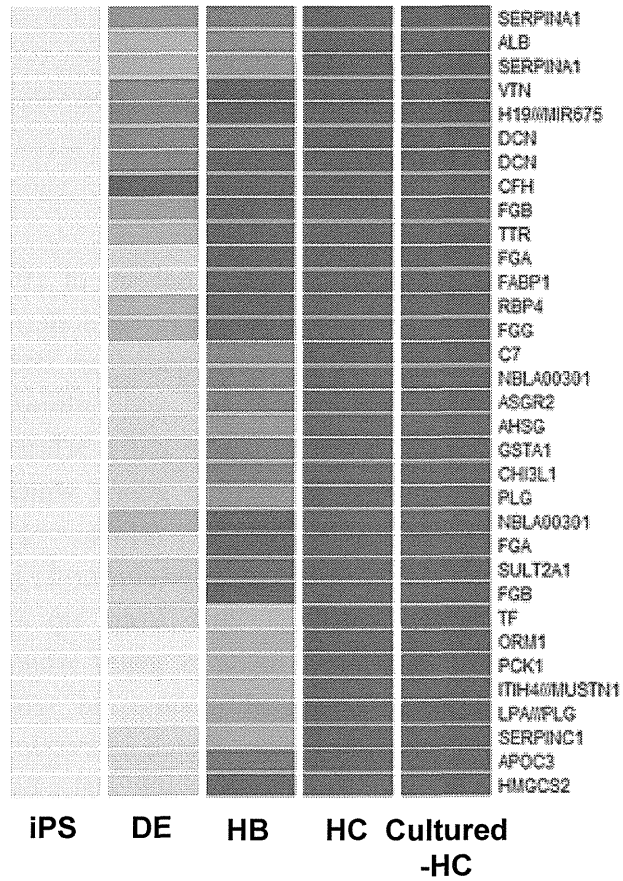

Fig.3 Hierarchical clustering analysis of iPS cells and iPS-derived definitive endoderm (DE), hepatoblast (HB), hepatocytes (just after differentiation or cultured; HC and cultured HC) for identification of HCV replication related genes. Cluster shown in this figure includes genes which expression increased gradually in differentiation process of iPS-derived HC. Yellow shows low expression, and red shows high expression. Gene names in this cluster are shown in right

column and table 3.

Gene Symbol	Gene name
CFH	complement factor H
H19///MIR675	H19, imprinted maternally expressed transcript
DCN	
DCN	
VTN	vitronectin
SERPINA1	serpin peptidase inhibitor
FGB	fibrinogen beta chain
FGG	fibrinogen gamma chain
SERPINA1	serpin peptidase inhibitor
RBP4	retinol binding protein 4, plasma
TTR	transthyretin (prealbumin, amyloidosis type I)
NBLA00301	Nbla00301
ALB	albumin
HMGCS2	3-hydroxy-3-methylglutaryl-Coenzyme A synthase 2
APOC3	apolipoprotein C-III
SULT2A1	sulfotransferase family, cytosolic, 2A
SERPINC1	serpin peptidase inhibitor, clade C (antithrombin), member 1
GSTA1	glutathione S-transferase A1
NBLA00301	Nbla00301
CHI3L1	chitinase 3-like 1 (cartilage glycoprotein-39)
FGB	fibrinogen beta chain
TF	transferrin
PLG	plasminogen
C7	complement component 7
FGA	fibrinogen alpha chain
AHSG	alpha-2-HS-glycoprotein
FABP1	fatty acid binding protein 1, liver
FGA	fibrinogen alpha chain
ASGR2	asialoglycoprotein receptor 2
PCK1	phosphoenolpyruvate carboxykinase 1 (soluble)
LPA///PLG	lipoprotein, Lp(a) /// plasminogen
ITIH4///MUSTN1	inter-alpha (globulin) inhibitor H4
ORM1	orosomucoid 1

Table 3 Gene names in Fig.3

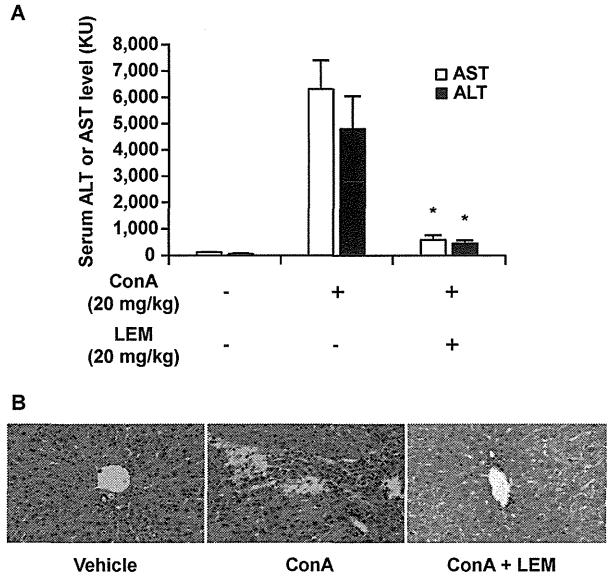

Fig.4 Effect of LEM against Concanavalin A (ConA) induced liver injury.

Mice were injected LEM (20 mg/kg body weight) or vehicle intraperitoneally and ConA (20 mg/kg body weight) or vehicle intravenously, and serum AST (open column) and ALT (closed column) levels were determined (A) or liver was stained with hematoxylin and eosin (B) 24 hours after injection. Data represent means ± SD (n=3, *P < 0.05 vs. ConA treated mice by dunnet). Magnification for all photographs, x400.

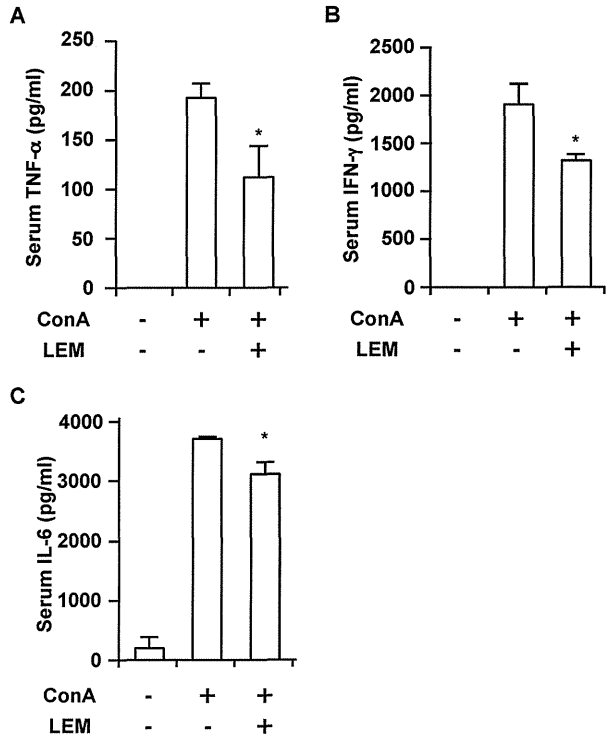

Fig.5 Changes in serum TNF-α, IFN-γ, and IL-6 levels by LEM in ConA induced liver injury model. Mice were injected LEM (20 mg/kg body weight) or vehicle intraperitoneally and ConA (20 mg/kg body weight) or vehicle intravenously, and serum TNF-α (A), IFN-γ (B) and IL-6 (C) were determined by ELISA. Data represent means ± SD (n=3, *P < 0.05 vs. ConA treated mice by dunnet).

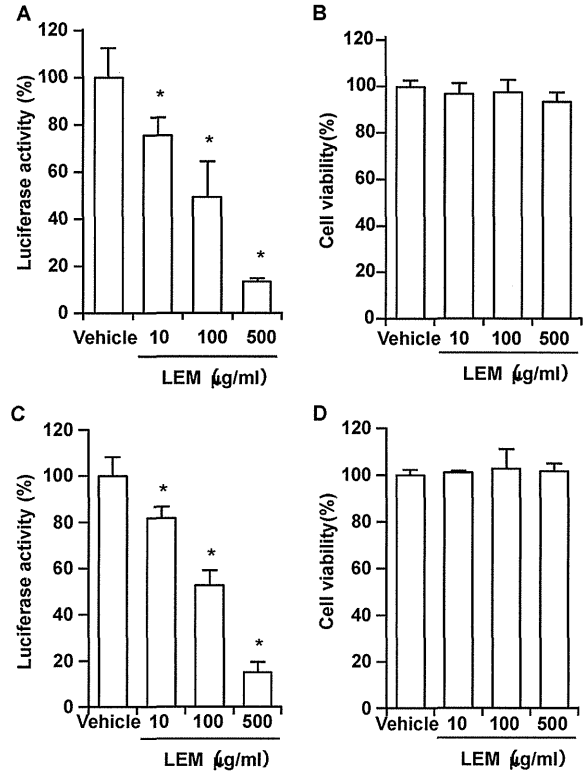

Fig.6 Anti HCV activity of LEM. Inhibition of HCV entry by LEM. Huh7.5.1 cells were infected with HCVpv (A, B: H77 C, D: Con1) and treated with LEM at same time. 24 hours after HCVpv infection, luciferase activity (A, C) and cell viability (B, D) were determined. All data represent means ± SD (n=3, *P < 0.05 vs. vehicle treated group by dunnet).

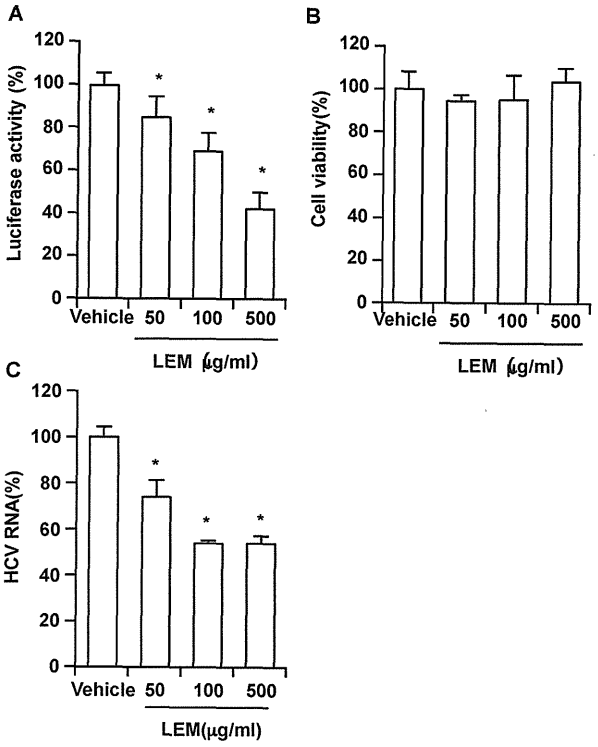

Fig.7 Anti HCV activity of LEM. Inhibition of HCV replication by LEM. Huh7.5.1 1bFeo cells, containing HCV subgenome replicon, were treated with LEM. 72 hours after treatment, luciferase activity (A), cell viability (B) and HCV RNA content were determined. All data represent means ± SD (n=3, *P < 0.05 vs. vehicle treated group by dunnet).

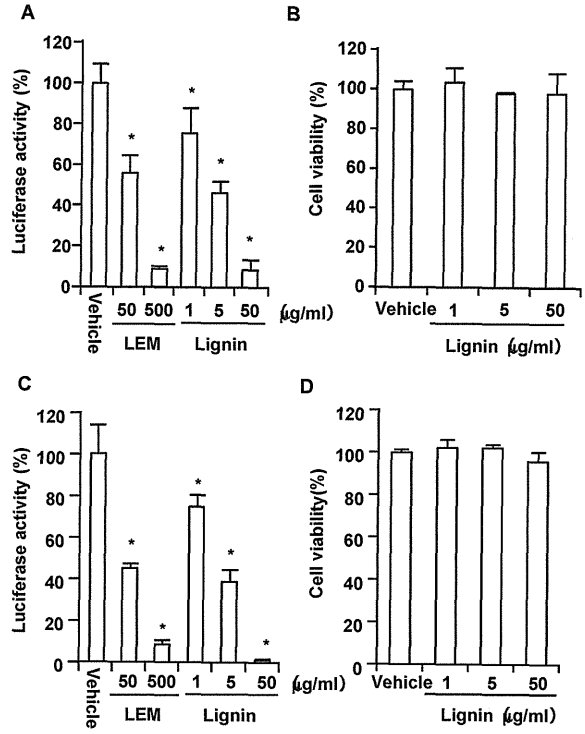

Fig.8 Inhibition of HCVpv entry by low-molecular-weight lignin. Huh7.5.1 cells were infected with HCVpv (A, B: H77, C, D: Con1) and treated with LEM or LM-lignin at same time. 24 hours after virus infection, luciferase activity (A, C) and cell viability (B, D) were determined. All data represent means ± SD (n=3, *P < 0.05 vs. vehicle treated group by dunnet).

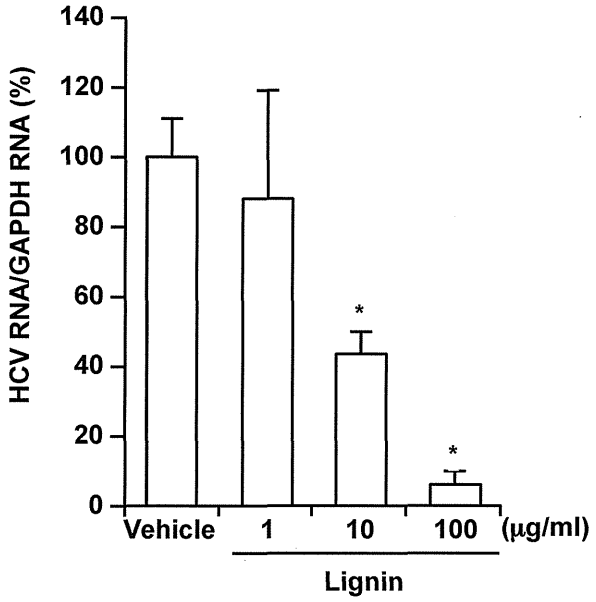

Fig.9 Inhibition of HCVcc entry by low-molecular-weight lignin. Huh7.5.1 cells were infected with HCVcc and treated with LM lignin at same time, and 2 hours after infection, HCVcc were washed out. 72 hours after HCVcc infection, HCV genome RNA and GAPDH mRNA were determined by real-time PCR. Data represent means ± SD (n=3, *P < 0.05 vs. vehicle treated group by dunnet).

Ⅲ．研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
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雑誌

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