

Table 1: 1111111

Category	Flavonoids	Models	Dose	Mechanism	Ref.
		BALB/c mice were subjected to exposure to CS for 2 h twice/day, 6 days/week for 4 weeks.	10, 20 mg/kg	Inflammatory cell↓in BALF; IL-1β↓, TNF-α↓in BALF and lung; MUC5AC↓in lung; p-EGFR↓, p-ERK↓, p-38↓	55
		CSE-induced NCI-H292 cells.	1, 2.5, 5, 10 μM	IL-1β↓, MUC5AC↓; p-EGFR↓, p-ERK↓, p-38↓	
	Phloretin	106 non-typeable <i>Haemophilus influenzae</i> , 105 CFU <i>Moraxella catarrhalis</i> , 5 105 CFU <i>Streptococcus pneumoniae</i> , and 105 CFU <i>Pseudomonas aeruginosa</i> strain PAO1 were grown with phloretin.	CFU 0.1-1 mM	Bacterial growth↓, pathogen biofilm formation↓	56
		3104 NTHi infected NCI-H292 cells.	0.1 mM	NTHi adhesion↓	
Chalcones		FVB/NJ mice were diet supplemented with phloretin (1 week) and were exposed intratracheally to NTHi (24 h).	0.157%	NTHi burden↓, CXCL1↓	
	Isoliquiritigenin	C57BL/6N male mice were subjected to exposure to CS for 2 h twice/day for 4 weeks.	10, 20, 30 mg/kg	Wet/Dry ratio↓, inflammatory cell↓; MPO↓, TNF-α↓, IL-1β↓in BALF; MDA↓in lung; p-p65↓, p-IκB↓in lung; Nrf2↑, HO-1↑in lung	57
		Male Wistar rats were subjected to exposure to CS for 1 h daily for 4 weeks, except received intratracheal instillation of LPS on the 1st and 14th day.	30, 48, 76.8 mg/kg	Wat/Pbm↓TGF-β1↓, α-SMA↓, Collagen I↓in lung; TGF-β1↓in plasma; p-p38↓in lung	58
	Hydroxysafflor yellow A	PAF-stimulated HSAECs.	9, 27, 81 μM	IL-6↓, IL-1β↓, TNF-α↓; PKC↓, p-ERK↓, p-JNK↓, p-p38, p-IκB↓	59
		Male Wistar rats were subjected to exposure to CS for 1 h/day for 4 weeks, except received intratracheal instillation of LPS on the 1st and 14th day.	30, 48, 76.8 mg/kg	IL-6↓, IL-1β↓, TNF-α↓in lung; ICAM-1↓, VCAM-1↓in lung; p-p38↓, p65↓in lung	60

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Category	Flavonoids	Models	Dose	Mechanism	Ref.
	Apigenin	H ₂ O ₂ -induced senescence of WI-38 cell.	10, 20 μ M	Senescence \downarrow	61
	Oroxylin A	Male C57BL/6 mice were subjected to exposure to CS for 1 h/day for 4 days.	6, 12, and 25 mg/kg	Inflammatory cell \downarrow in BALF; TNF- α \downarrow , IL-1 β \downarrow , MCP-1 \downarrow in BALF; 3-NT \downarrow , 8-OHdG \downarrow , 8-isoprostane \downarrow ; GSH \uparrow , Nrf2 \uparrow , HO-1 \uparrow , GR \uparrow , GPX-2 \uparrow	62
		CSE-induced RAW264.7.	50, 100, 150 μ M	TNF- α \downarrow , IL-1 β \downarrow , Nrf2 \uparrow , HO-1 \uparrow	
		RSL-3 or Erastin-induced human BEAS-2B cells.	1, 2, 5 μ M	LDH \downarrow , HMGB \downarrow ; lipid ROS \downarrow , MDA \downarrow , GSH \uparrow , GPX4 \uparrow , HMOX1 \downarrow , ATF3 \downarrow , Keap1 \uparrow , Nrf2 \downarrow , HO-1 \downarrow , p-JNK \downarrow , p-p38 \downarrow	
	Scutellarein	Male C57BL/6 mice were subjected to exposure to CS for 1 h/day for 6 weeks, except received intratracheal instillation of LPS on the 1st and 14th day.	5, 10, 20 mg/kg	TNF- α \downarrow , IL-1 β \downarrow , IL-6 \downarrow in serum; HMGB1 \downarrow in BALF; MDA \downarrow , GPX4 \uparrow in lung tissues; HMOX1 \downarrow , HO-1 \downarrow	63
		C57BL/6 mice were exposed to elastase and LPS on day four of the week for four weeks.	10 mg/kg	Lung function \uparrow ; TBARS, Hmox-1, KC/CXCL-1 \downarrow , MIP-2/CXCL-2 \downarrow , MCP-1/CCL2 \downarrow , IL-1 β \downarrow , IL-12p40 \downarrow , MIP-1 β \downarrow , MUC5AC \downarrow , MMP-9 \downarrow , MMP-12 \downarrow , SIRT1 \uparrow	64
		CSE-induced U937 cells peripheral blood mononuclear cells (PBMC) collected from patients.	10 μ M	TNF α \downarrow , CXCL8 \downarrow , p-AMPK \uparrow , Nrf2 \uparrow , corticosteroid insensitivity \uparrow	65
Flavones	Quercetin	Female mice were subjected to whole body CS for 2h/day, 5 days/week for 8 weeks, and received intratracheal instillation of NTHi on the 7th and 21st day, and infected with RV.	100 mg/kg	CXCL-1 \downarrow , CXCL-10 \downarrow , TNF- α \downarrow , IFN- \downarrow and IL-17A \downarrow CD11b+CD11c+ macrophages \downarrow , neutrophils \downarrow , CD8+T cells \downarrow	66
		Male SD rats were subjected to exposure to CS for 1 h/day for 3 months.	50 mg /kg	Lung function \uparrow ; Caspase-3 \downarrow , Caspase-9 \downarrow in lung; IL-6 \downarrow , TNF- α \downarrow , IL-10 \uparrow in serum; TGF- β 1 \downarrow , α -SMA \downarrow in lung	67
		COPD patients	2,000 mg/day	Lung function \uparrow	68

Table 1: 1111111 (Continued)

Category	Flavonoids	Models	Dose	Mechanism	Ref.
		Female C57BL/6 mice were subjected to exposure to CS for 30 min four times a day for 14 d.	1, 2, 10 mg/kg	Inflammatory cell↓in BALF; TNF-α↓, IL-6↓, IL-1β↓, KC↓, MCP-1↓in BALF	75
	Casticin	Male Wistar rats were subjected to exposure to CS twice/day for 85 days.	10, 20, 30 mg/kg	Lung function↑; inflammatory cell↓in plasma; leptin↑C-reactive protein↓in plasma; MDA↓, GSH↑, SOD↑, TNF-α↓, IL-1β↓, IL-6↓, TLR4↓, p-NF-κB↓, p-IκBα↑in lung	76
		LPS-induced BEAS-2B cells.	0.5, 1, 2, 5, 10 μM	IL-1β↓, TNF-α↓, IL-6↓, IFN-↓, apoptosis cell↓, p-p65↓, Nrf2↑, keap-1↓	77
		H ₂ O ₂ induced BEAS-2B cells.	0.5, 1, 2, 5, 10 μM	ROS↓, SOD↑, MDA↓, Nrf2↑, HO-1↑, Keap-1↓	78
		Male BALB/c mice were exposed first to 100 mg/m ³ CS for 15 days and then to 250 mg/m ³ CS for 5 days/week for 75 consecutive days (6 h/day).	20, 40 mg/kg	Body weight, SOD↑, CAT↑, and MDA↓in serum and BALF; IL6↓, IL1β↓, IL8↓, TNFα↓in serum and BALF; NQO1↑, HO1↑; pp65↓pIκB↓, NOX4↓	79
		CSE-treated A549 cells.	100, 200 μM	SOD↑, CAT↑, MDA↓, IL6↓, IL1β↓, IL8↓, TNFα↓NQO1↑, HO1↑, pp65↓pIκB↓, NOX4↓	
	Luteolin	CSE-treated A549 cells.	10, 30 μM	SOD↑, LDH↓, and MDA↓, ROS↓, mitochondrial ROS↑, Ca ²⁺ influx↓, TRPV1↓, SIRT6↑, CYP2A13↓, NRF2↑, PGC1α↑, SOD1↑, SOD2↑	
Flavones		C57BL/6J mice intratracheal injections of LPS on the 1 st and 14 th days of the trial. Mice were passively exposed for 15 min, twice/day, six days/week, for eight weeks.	50, 100 mg/kg	Body weight↑, lung index↓, SOD↑, LDH↓, MDA↓, CAT↑, GSH↑, TRPV1↓, SIRT6↑, CYP2A13↓, NRF2↑, PGC1α↑, SOD1↑, SOD2↑	80
		Hartley strain guinea pigs were subjected to exposure to CS 1 h/day, 6 days/week, for 8 weeks.	9.2, 18.4, 36.8 mg/kg	Inflammatory cell↓in BALF; SOD in lung, MPO in lung and BALF	81
		BALB/c mice were subjected to exposure to CS for 1 h/day for 90 days.	20, 40, 80 mg/kg	Lung function↑; TNF-α↓, IL-8↓, MMP-9↓in lung and BALF; p-p65↓, IκB-α↓, GR	82

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Category	Flavonoids	Models	Dose	Mechanism	Ref.
Flavones	Taxifolin (dihydroquercetin)	Mice were subjected to exposure to CS 1 h twice/day, 6 days/week for 4 weeks with Days 0, 11, and 22; the mice were intraperitoneally injected with 0.3 mL/20 g 100% CSE.	50, 100 mg/kg	SLC7A11↑, MDA↓, SOD↑	GPx4↑, 86
		CSE-treated HBE cells.	40, 80 μ M	MDA↓, SLC7A11↑, Nrf2↑, lipid peroxidation↓	SOD↑, GPx4↑, 87

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Category	Flavonoids	Models	Dose	Mechanism	Ref.
Flavone glycosides	Baicalin	Male SD rats were subjected to exposure to CS for 40 min, twice/day, 5 days/week, for 5 weeks.	20, 40, 80 mg/kg	Lung function↑; inflammatory cell↓in BALF; IL-6↓, IL-1β↓, TNF-α↓in serum and BALF; p65↓in lung	88
		CSE-treated human type II pneumocytes.	5, 10, 20 mM	IL-6↓, IL-1β↓, TNF-α↓, p-p65↓, IκB-α↑	
		Male BALB/c mice exposed CS for 1 h/day, 6 days/week for 3 months.	25, 50, 100 mg/kg	Lung function↑; IL-8↓, MMP-8↓, TNF-α↓in serum and BALF; HDAC2↑, p-HDAC2↓	89
		CSE-treated A549 cells.	10, 50, 100 μM	IL-8↓, HDAC2↑	
		SD rats were subjected to exposure to CS for 1 h, 3 times/day, 6 days/week for 36 months.	40, 80, 160 mg/kg	Lung function↑; IL-1β↓, IL-6↓, and IL-10↑, TNF-α↓, IL-17, MMP-2↓, MMP-9↓, TIMP-1↑, MDA↓, T-AOC↑, SOD↑, HO-1↓, blood pH and PaO ₂	90
		Male C57BL/6N mice were subjected to exposure to CS of 1 h for 7 days and administered LPS via nasal instillation.	25, 50, 100 mg/kg	MUC5AC↓, IL-6↓, IL-8↓, TNF-α↓in the BALF; JNK↓but HSP72 inhibitor revise all	91
		CSE-treated MLE-12 cells.	5, 10, 20 μM	HSP72↓, apoptosis cell↓	
		Si-HSP72 treated / MLE-12 cells.	/	Apoptosis cell↑, IL-6↑, IL-8↑, TNF-α↑	
		SD rats exposed CS for 1 h/day, 6 days/week, for 24 weeks.	40, 80, 160 mg/kg	Lung function↑TNF-α↓, IL-1β↓in lung and serum; p-p65↓p-IκB-α↑, HDAC2↑PAI-1↓	92
		CSE-treated HBE cells.	10, 20, 40 μM	Cells viability↑; TNF-α↓, IL-1β↓, p-p65↓, p-IκB-α↑, HDAC2↑, PAI-1↓	
LPS-treated HBE cells.	10, 50, 100 μM	Cell apoptosis↓; TNF-α↓, IL-6↓, P21↓, Bax↓, cyclinD1↑, Bcl2↑, miR4451↑	93		
IL-1βtreated H292 cells.	NCI-200 μg/mL	IL-8↓, TNF-α↓, p65↓, IκB↑, MUC5AC↓, CFTR↑	94		
Male SD rats were subjected to exposure to CS for 1 h/day for 4 weeks, except received intratracheal instillation of LPS on the 1st and 14th day.	40, 80, 160 mg/kg	Lung function↑; TNF-α↓, IL-1β↓, IL-6↓, IL-8↓, IL-10↓in serum; GSH↑, SOD↑, MDA↓in serum; TLR2↓, MYD88↓, TNF-α↓, and IL-1β↓in BALF cells; NF-κB↓, TLR2↓, MYD88↓,	95		

Table 1: 1111111 (Continued)

Category	Flavonoids	Models	Dose	Mechanism	Ref.	
Flavone glycosides	Astragalgin	Male BALB/c mice were subjected to exposure to CS for 30 min once a day for 8 weeks.	10, 20 mg/kg	Inflammatory cell↓in BALF; PAR-1↓, PAR-2↓, Tpa↑, PAI-1↓	97	
		Thrombin-exposed A549 cells.	1, 10, 20 μM	PAR-1↓and PAR-2↓, Tpa↑, PAI-1↓Upa↓, ICAM-1↓, COX-2↓, iNOS↓, p-P38↓, p-JNK↓, p-ERK↓		
		CSE-treated BEAS2B cells.	20, 40, 80 μM	IL8↓, TNFα↓, IL-10↑; ROS↓, MMP-9↓, TIMP1↑, GR↑, HDAC2↑, NF-κB↓, Nrf2↑		98
	Icariin	SD rats were subjected to exposure to CS for 40 min, 5 days/week, 8 weeks.	2.12 mg/kg (icariin to no-biletin 12.5:1)	Lung function↑; IL-6↓, IL-1β↓, TNF-α↓in lung; PI3K↓, p-AKT↓, p-p38↓in lung	99	
		CSE-treated NCI-H292 cells and BEAS-2B cells.	25, 50, 75 μM	PPAR↑, NF-κB p65/lamin-B↓, NF-κB p65↑, IκB-α↑, IL-6↓, TNF-α↓in BALF or serum	100	
	Liquiritin apioside	Male SD rats were subjected to exposure to CS.	40 mg/kg	Lung function↑, PPAR↑, p65↓, IκB-α↓	101	
		Female ICR mice were subjected to exposure to CS for four days.	3, 10, 30 mg/kg	Inflammatory cell↓in BALF; MPO↓in lung; TNF-α↓, TGF-β↓, SOD↑		
		CSE-induced A549 cell.	0.1, 1 μM	TGF-β↓, TNF-α↓, apoptosis cell↓		
		EGF-simulated NCI-H292 cell.	5, 10, 25, 50 μM	P-AKT↓, p-p38↓, p-ERK↓, p-MEK↓, MUC5AC↓, p-Sp1↓		102
		EGF-simulated A549 cell.	5, 10, 25, 50 μM	P-AKT, p-p38, p-ERK, p-MEK, p-Sp1↓		
Tilianin	Male BALB/c mice were administered 100 μL of CFD in saline by intratracheal instillation thrice at 3-day intervals for 12 days using bronchial tubes.	10 mg/kg	CXCL2↓, IL-17A↓, CXCL1↓, and TNF-α↓in BALF; SDMA↓in serum; CXCL2↓, IL-17A↓, CXCL1↓, MUC5AC↓, IL-6↓, TNF-α↓NOS-II↓, TRPV1↓, STAT3↓in lung; neutrophil infiltration↓in lung and BALF	103		
	CFA-induced the mouse epithelial cell line LA-4 and human mast-cell line HMC-1.	50 μg/mL	CXCL2↓, IL-17A↓	8		
Naringin	Hartley strain	18.4 mg/kg	Cough↓, pause↓; SP↓, NEP↓, iNOS↑, NK1↓	104		

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Category	Flavonoids	Models	Dose	Mechanism	Ref.
Isoflavones	Biochanin A	Male SD rats received intratracheal instillation of PM _{2.5} once every five days for five times.	25, 50, 100 mg/kg	SOD↑, CAT↑in lung; GSH-Px↑, ALB↓in serum; TNF-α↓, IL-2↓, IL-6↓, IL-8↓in lung; MDA↓in serum; AKP↓, LDH↓in BALF; XRCC1↓, MAP2K5↓, IGJ↓	105
		CSE-induced HBE cell.	50, 100, 200 μg/mL	Apoptosis↓, caspase3↓, MMP level↑mitochondrial ROS↓, ATP↑, PINK1↓, Parkin↓, DRP1↓, FUNDC1↓, p-FUNDC1↑	106
	Puerarin	Male Wistar rats were subjected to exposure to CS for 1 h/day for 4 weeks, except received intratracheal instillation of LPS on the 1st and 14th day.	50, 100, 200 mg/kg	Lung function↑, TNF-α↓, IL-1β↓, IL-6↓in BALF; apoptosis↓in lung; BECN1↓, LC3B↓in lung; parkin↓, Bax↓, Bcl-2↑in lung	107
Isoflavones	Formononetin	Male C57BL/6J mice were subjected to exposure to CS of 9 cigarettes/h, 4 h/day, 6 days/week for 24 weeks.	50 mg/kg	Total cells↓, macrophages↓, and neutrophils↓in BALF; TNF-α↓, CXCL1↓in BALF; IL-10↓, CCL22↓in lung; Apoptosis: Bcl-2↑, Bax↓, cleaved caspase 3↓in lung; Endoplasmic reticulum stress: GRP78↓, CHOP↓, ATF6↓, p-ERK↓, p-EIF2α↓, AhR↓, CYP1A1 ↓, p-AKT↓, p-mTOR↓	108
		CSE-exposed BEAS-2B.	50 μM FMN	Inflammation: TNF-α↓, IL-1β↓, IL-8↓Apoptosis: apoptotic cells↓, Bax↓, cleaved caspase↓ER stress: GRP78↓, CHOP↓, ATF6↓, p-EIF2α↓, p-ERK↓, AhR↓, CYP1A1↓, p-AKT↓, p-mTOR↓	

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Category	Flavonoids	Models	Dose	Mechanism	Ref.
Flavanols	-Epicatechin	Wistar male rats were subjected to exposure to CS for 1 h twice/day for 12 weeks.	5, 15, 45 mg/kg	MDA↓, IL-1β↓ in BALF; HO-1↑, NQO1↑, SOD1↑, SOD2↑, SOD3↑, NLRP3↓, GSDMD-N↓, caspase-1↓, IL-18, IL-1β	109
		CSE-induced BEAS-2B cells.	10, 20, 50 μM	MDA↓, Keap1↓, Nrf2↑, HO-1↑, NQO1↑, NLRP3, GSDMD-N, caspase-1, IL-18, IL-1β	
	Epigallocatechin gallate	CSE-induced NHBE cell.	5, 10, 20 μM	ROS↓, lipid peroxidation↓, 4-HNE-protein adduct↓, p65↓, COX-2↓, NOX4↓, NOS2↓, IL-6↓, IL-8↓	110
Bisflavonoid	Ginkgetin	C57 mice were subjected to exposure to CS of 0.5 h twice/day for 10 weeks, and LPS airway instillation on days 1, 14, 28, and 42 d.	10, 40 mg/kg	IL-6↓, IL-17A ↓, TNF-α↓, in BALF; FEV0.1/FVC↑	115
Other Flavonoids	Silibinin	CSE-induced A549 cell.	50, 100, and 250 μg/mL	C/EBPβ↓, CCL2↓	
		Male C57BL/6N mice were subjected to exposure to CS of 1 h/day for 7 days.	25, 40 mg/kg	Inflammatory cell↓; IL1β↓, IL6↓, MUC5AC↓ in BALF; p-ERK↓, SP1↓	111
	Silymarin	CSE-induced NCI-H292 cells.	6.25, 12.5, 25, 50 μM	IL6↓, MUC5AC↓, p-ERK↓, SP1↓	
		Male C57BL/6N mice were subjected to exposure to CS of 1 h/day for 4 weeks.	10, 20 mg/kg	Inflammatory cell↓, IL1β↓, IL6↓, TNF-α↓ in BALF; TGF-β1↓, collagen↓, p-Smad 2/3↓	112
Silymarin	Silymarin	BALB/c mice were subjected to exposure to CS of 2 h twice/day, 6 days/week for 4 weeks.	25, 50 mg/kg	Inflammatory cell↓; IL1β↓, IL6↓, TNF-α↓ in BALF; p-p38↓, p-ERK↓, MDA↓, SOD↓	113
		CSE-exposed BEAS-2B.	10, 20 μM	P-p38↓, LC3II/I↓, p-ERK↓	114

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Table 1: 1111111 (Continued)

Category	Flavonoids	Models	Dose	Mechanism	Ref.
Total flavonoids	Total flavonoids of <i>Nigella glauca</i> Freyn et Sint.	Papain nebulization inhalation for 4 weeks, and LPS airway instillation on the 1st and 15th days.	71.5, 286 mg/kg	Inflammatory TNF- α ↓, NF- κ B↓in BALF	cell↓, IL-8↓, 116
	Total flavonoids of sea buckthorn	Male ICR mice were subjected to exposure to CS for 1 h/day for 30 days and received intratracheal instillation of LPS on the 1st and 14th day.	100, 200, 500 mg/kg	Inflammatory BALF; IL1 β ↓, COX2↓, CXCL1↓in lung	cell↓in IL6↓, MUC5AC↓, 117
		LPS/CSEactivated HBE16 cells.	10, 20, and 50 μ g/mL	IL1 β ↓, IL6↓, CXCL1↓, MUC5AC↓, PGE2↓, p-ERK↓, p-Akt↓, p-PKC↓	

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Table 1: 1111111 (Continued)

Category	Flavonoids	Models	Dose	Mechanism	Ref.
	Total flavonoids from <i>Scutellaria Baicalensis</i> Georgi	Male ICR mice were subjected to exposure to CS for 1 h/day for 28 days and received intratracheal instillation of LPS on the 1st and 14th day.	25, 50 mg/kg	Inflammatory cell↓, IL-6↓, IL-8BALF; MDA↓, SOD↑, SIRT1↑, PGC-1α↑in lung	118
	Total flavonoids of Loquat leaves	Male C57BL/6 mice were subjected to exposure to CS four times/day, 5 days/week for 12 weeks.	50, 100 mg/kg	Body weight↑and lung index↓; TRPV1↓in lung; IL-1β↓, IL-6↓, TNF-α↓, NO↓, SOD↑, MDA↓in the serum; p-IKK↓, p-IκB↓, p-p65↓, p-Akt↑, iNOS↓, CYP2E1↓, p-JNK↓SOD-2↑	119
Total flavonoids	Total flavonoids of <i>Trollius altaicus</i>	Male Wistar rats were subjected to exposure to CS for 1 h/day for 45 days and received intratracheal instillation of LPS on the 1st and 15th day.	125, 250, 500 mg/kg	Lung function↑, W/D↓; inflammatory cell↓in blood; IL-1β↓, IL-6↓, IL-8↓, IL-10↑, TNF-α↓, TGF-1β↓in BALF; TLR4↓, IKKα↓, p65↓, IL-1β↓in lung; IRAK-1↓, IKKα↓, p65↓, IL-1βlung	120
	Total flavonoids of <i>Trollius altaicus</i>	Old male C57BL/6 mice were subjected to exposure to CS for 40 min twice/day for 4 weeks and received intraperitoneal injections of CSE on the 1st, 12th, and 23rd days.	125, 250, 500 mg/kg	P-p38 MAPK↓, p-ERK1/2↓in lung	121
	Total flavonoids of Dandelion	Female BALB/c mice were subjected to exposure to CS for 1 h/day for 12 weeks.	2, 25, 4.5 g/kg	Lung function↑; SOD↑, GSH↑, MDA↓, Nrf2↑, SOD1↑, HO-1↑	122

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