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The immune-modulatory potential of helminth-derived proteins in cellular models of inflammation: a systematic review with cross-study quantitative data analysis

Sienna Stucke[1], Aonghus Feeney[1], Richard Lalor[2], Sheila Donnelly[2], John Pius Dalton[2], Declan McKernan[1] & Eilís Dowd[1]✉

Helminths are parasitic worms that secrete a plethora of immune regulatory molecules which allow them to moderate inflammatory responses by their host's immune system to ensure their survival within the host. This ability to drive a compatible existence with their host has led to research into the potential therapeutic effects of helminth-derived molecules the regulation of overactive immune and inflammatory responses in a wide variety of diseases. This systematic review with cross-study quantitative data analysis aims to synthesize the published data on helminth-derived immunomodulatory peptides/polypeptides/proteins (HDIPs) with a focus on determining the extent to which they modulate the inflammatory response in in vitro cellular models of inflammation. In accordance with PRISMA 2020 guidelines, a predefined systematic search of the PubMed, Web of Science and Medline databases identified relevant studies published up to September 2025, and 79 articles were included after screening. We found that most published studies used LPS or Concanavalin A stimulated macrophages, peripheral blood mononuclear cells or dendritic cells as the cellular model of inflammation. Twenty helminth species from which > 60 isolated HDIPs were derived were tested in these models, with the nematodes, *Haemonchus contortus* and *Acanthocheilonema viteae*, and the trematode, *Fasciola hepatica*, the most explored species. A common property of these molecules was the ability to significantly reduce the expression or production of pro-inflammatory cytokines such as IL-12, IL-1β, IL-6 and TNF, and significantly increase the expression or production of anti-inflammatory cytokines such as IL-10, TGFβ and IL-4. The effects on other cytokines, including IFNγ which is known to have both pro- and anti-inflammatory effects, were less consistent, with HDIPs either decreasing or increasing the levels of this cytokine. This systematic review with cross-study quantitative data analysis synthesizes the existing literature in this field and shows that the HDIPs secreted by several helminth species have consistently demonstrated effects though modification of cytokine levels and, as such, have therapeutic potential in conditions in which overactive immune and inflammatory responses play a pathogenic role.

Keywords Parasitic worms, Helminth, Helminth-derived peptides, Inflammation, Cytokines

Helminths are parasitic worms, classified into nematodes (roundworms, whipworms and hookworms), trematodes (blood-flukes) and cestodes (tapeworms)[1]. These parasites are able to infect a wide variety of species and can cause mild to severe disease in their hosts. Soil-transmitted helminth infections, considered the most important group of neglected tropical diseases by the World Health Organization (WHO), are typically caused by nematode parasites and can lead to intestinal issues, kidney damage, dermatitis, respiratory issues, allergy symptoms, malnutrition, fatigue and other health issues[2]. The parasite eggs are deposited through human and animal faeces where the larvae can survive in water or soil for weeks until they are ingested (or otherwise enter

[1]Pharmacology & Therapeutics, Galway Neuroscience Centre, Institute for Health Discovery and Innovation, School of Pharmacy and Medical Sciences, University of Galway, Galway, Ireland. [2]Molecular Parasitology Laboratory, Centre for One Health, Ryan Institute, School of Natural Sciences, University of Galway, Galway, Ireland. ✉email: eilis.dowd@universityofgalway.ie

the body) and then migrate into the intestines, liver, or other tissues where they mature, develop and lay eggs to complete the growth cycle[3]. It is estimated that over 1.5 billion people around the world are infected with one or more of these helminth species, with infections affecting those in developing countries at higher rates due to poor sanitation facilities and infected drinking water[2].

Interestingly, in developed or high-income countries where worm infections are low, there has been notable increases in immune-mediated conditions such as colitis, allergy and eczema in recent decades that align with patterns of decreasing helminth infection[4,5]. This inverse correlation between helminth infection and immune/inflammatory disease suggests that by limiting exposure to the diverse pathogens through safer hygiene and sanitation practices, more humans today lack the immune-protective effects provided by helminth infection against inflammatory and allergenic diseases[6]. This idea has evolved into the 'old friends' hypothesis, proposing that, because helminths evolved alongside the adaptive immune system they provide some protection against certain diseases, and in their chronic infective state, they are more like 'old friends' than foe[7]. Indeed, in endemic populations it seems the ubiquitous presence of helminths has even impacted the immune response at the genome level with evidence of SNP in genes associated with the Th2 immune response[8]. These observations have stimulated extensive research into elucidating the molecular mechanisms behind the immunomodulatory properties of worms, and particularly the molecules they secret as a potential novel source of biotherapeutics for the treatment of immune and inflammatory conditions.

Although helminth infections can be detected and ejected by the host immune system (primarily through IL-4-driven Th2 responses[9]), they can also secrete a plethora of immune-modulatory molecules which can allow then to remain undetected for long periods of time by their host's immune system[10]. These helminth-derived immunomodulatory peptides/polypeptides/proteins (HDIPs) can modulate the host's immune response by shifting the balance between the Th1 and Th2 responses. This can lead to a state of immune tolerance during the parasite's chronic infective stage, allowing them to remain tolerated by the host for months, years or even decades. While HDIPs are secreted for parasite protection inside the host, because they are immunosuppressive, they may have therapeutic potential as isolated (or synthetic) peptides/polypeptides/proteins in a wide variety of diseases in which overactive immune and inflammatory responses play a pathogenic role[1,11]. Multiple types of HDIPs from a variety of helminth species have been isolated and purified (or synthesized) in the past twenty years. These have been shown to modulate the immune and inflammatory response in multiple cell types, particularly through altered cytokine responses. However, to date, there has been no systematic review of this literature, and thus, this review aims to systematically synthesize the published data on HDIPs and the extent to which they modulate the inflammatory response in cellular models of inflammation.

Methods

Search strategy

This study was completed in accordance with the PRISMA 2020 guidelines[12] to find articles in which HDIPs were assessed in cellular models of inflammation. The literature search was completed in the PubMed, Web of Science and Medline databases with the specific search string: helminth AND secret* AND (immunomod* OR immunosup* OR antiinflam*). This search identified a total of 781 records, spanning July 2001 to September 2025. These articles were then screened according to the strategy outlined below and depicted in the PRISMA flow diagram (Fig. 1). This yielded 79 articles which were included in this systematic review. All records were managed in the Endnote and Microsoft Excel software packages.

Screening strategy

Once all duplicate records were removed, the remaining articles were screened by title and abstract according to the following inclusion and exclusion criteria. Inclusion criteria: (1) original research study, (2) HDIPs, (3) cellular inflammatory model. Exclusion criteria: (1) review article, (2) not helminth-derived (3), undefined helminth-derived molecule, (4) not peptide/polypeptide/protein helminth-derived molecule, (5) not tested in inflammatory model and (6) not peer-reviewed or redacted. In the full-text screen, three other exclusion criteria were applied (7) no cytokine measure, (8) no appropriate control and (9) not in a cellular (in vitro) model. After screening, 63 articles met the inclusion and exclusion criteria. The reference lists in these articles were then further screened by title, and those naming a specific species (rather than using the term "helminth") were further screened using the same inclusion and inclusion criteria as the other articles. This led to inclusion of a further 16 articles. Thus, a total of 79 articles were included in this systematic review (Table 1 and Supplementary Excel file).

Data extraction

Variables manually extracted from the selected articles included cell type, inflammagen, helminth species and HDIP name, as well as cytokines measured (Table 1 and Supplementary Excel file). Because any given article may have had several experimental parameters (e.g. different HDIP concentrations or different incubation times etc.), to comprehensively synthesize this literature, each of these was considered a separate "record" for cytokine data analysis. Cytokine levels were measured by qPCR, Western immunoblotting or ELISA, and expressed as relative values or concentration as appropriate. Specific values were extrapolated from the relevant figure(s) within each article using GetData Graph Digitizer software. Based on the data extracted, we determined that a formal meta-analysis was inappropriate due to substantial heterogeneity across studies[13], including differences in helminth species, helminth-derived peptides, cell models, inflammagens, cytokines assessed, analytical methods, and specific experimental design parameters. Instead, we conducted a cross-study quantitative analysis focusing on the percent change in inflammagen-induced cytokine levels following treatment with helminth-derived peptides. To do so, the effects of the HDIPs were quantitatively assessed by calculating the percent change in

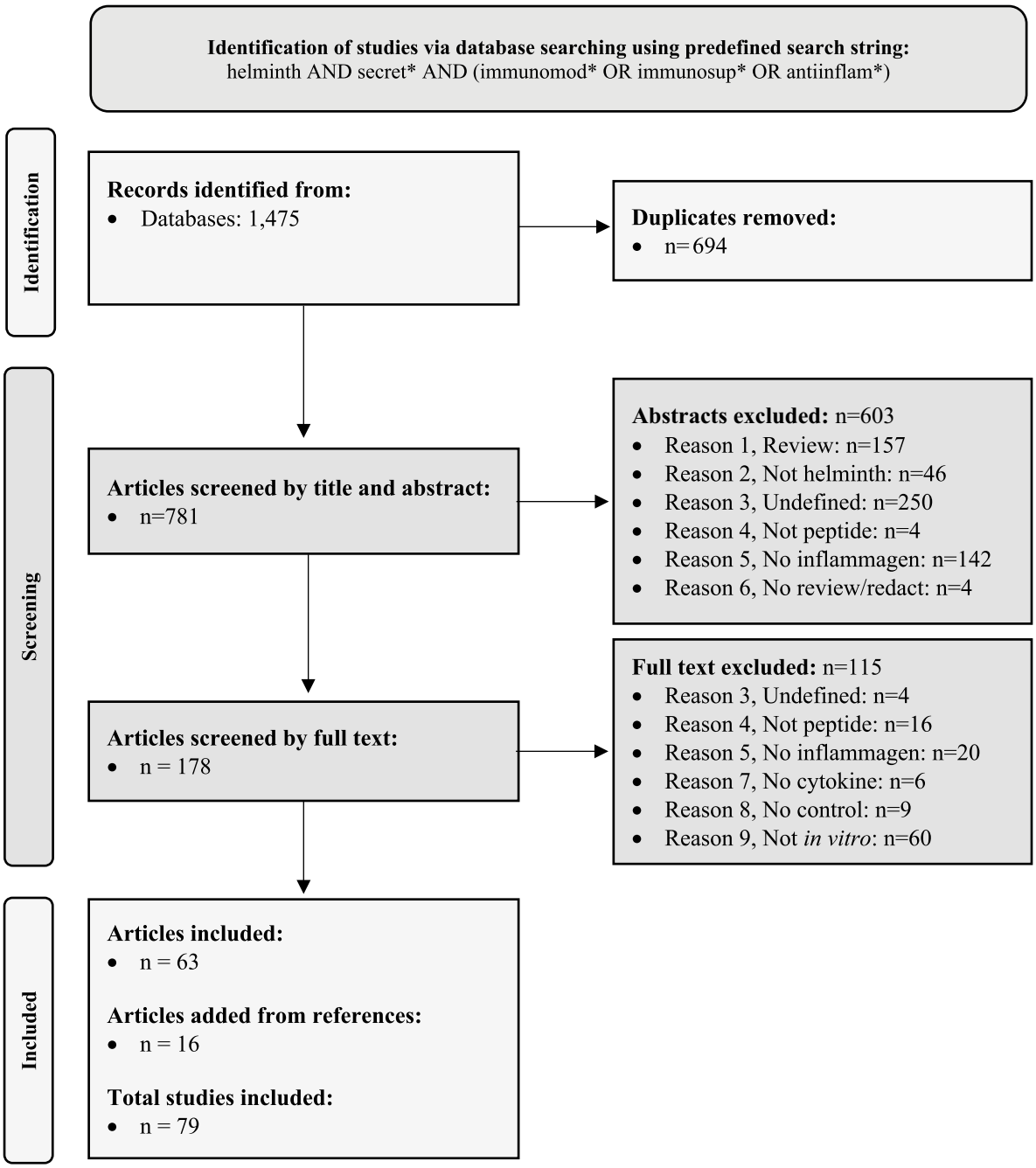


Fig. 1. PRISMA flow chart. Flow chart based on PRISMA 2020 guidelines[12] detailing the screening strategy employed for the study selection in the present study.

cytokine levels when cells were challenged with inflammagen in the absence versus the presence of the HDIPs. Data extraction was completed independently by two of the authors (SS and AF) and cross-checked for accuracy.

Statistical analyses

General study characteristics are shown as pie charts. All data related to percent cytokine change are shown as scatter plots depicting individual records with the mean ± standard error of the mean (SEM). To determine if the HDIPs reduced or increased cytokine levels beyond zero, data were analysed using one-sample t-test (with the hypothesised population mean set to zero). To determine the effect of cell type, inflammagen or cell species on the efficacy of HDIPs, the data were analysed by two-way ANOVA with *post-hoc* Bonferroni. The reader is also directed to the Supplementary Excel File where the extracted data is provided in more detail and can be sorted, filtered and/or pivoted for further analyses.

References	Author	Cell type(s)	Inflamm (s)	Helminth (s)	HDIP	[HDIP] (μg/ml)	Time (hr.)
[14]	Schönemeyer 2001	hPBMC	Anti-CD3	*O. volvulus*	rOv17	0.5 μM	48
[15]	Goodridge 2001	mMacrophage	LPS & IFNγ	*A. viteae*	ES-62	1	18
[15]	Goodridge 2001	mMacrophage	LPS & IFNγ	*A. viteae*	ES-62	2	18
[15]	Goodridge 2001	mMacrophage	LPS & IFNγ	*A. viteae*	ES-62	5	18
[16]	Spolski 2002	mT cell	ConA	*T. crassiceps*	p66	20	72
[17]	McInnes 2003	hT cell	LPS	*A. viteae*	ES-62	2	18
[17]	McInnes 2003	hT cell	Type II collagen	*A. viteae*	ES-62	2	18
[18]	Goodridge 2005	mMacrophage	LPS & IFNγ	*A. viteae*	ES-62	2	18
[18]	Goodridge 2005	mMacrophage	LPS & IFNγ	*A. viteae*	ES-62	2	18
[18]	Goodridge 2005	mDendritic cell	LPS	*A. viteae*	ES-62	2	18
[19]	Rigano 2007	hDendritic cell	LPS	*E. granulosus*	EgAgB	10	18
[20]	Donnelly 2008	mSplenocyte	PMA & Anti-CD3	*F. hepatica*	rFhPrx	20	72
[21]	Brännström 2009	hMonocyte	LPS	*S. mansoni*	rSm16	20	6
[21]	Brännström 2009	hMonocyte	LPS	*S. mansoni*	rSm16	20	8
[21]	Brännström 2009	hMonocyte	Poly I:C	*S. mansoni*	rSm16	20	6
[21]	Brännström 2009	hMonocyte	Poly I:C	*S. mansoni*	rSm16	20	8
[22]	Sun 2012	mSplenocyte	PMA	*S. japonicum*	rSj16	0.5	72
[23]	Chhabra 2014	hT cell	Thapsigargin	*A. caninum*	AcK1t	0.3 μM	48
[23]	Chhabra 2014	hT cell	Thapsigargin	*A. caninum*	AcK1t	15 μM	48
[23]	Chhabra 2014	hT cell	Thapsigargin	*A. caninum*	AcK1t	3 μM	48
[23]	Chhabra 2014	hT cell	Thapsigargin	*B. malayi*	BmK2	0.01 μM	48
[23]	Chhabra 2014	hT cell	Thapsigargin	*B. malayi*	BmK2	0.1 μM	48
[23]	Chhabra 2014	hT cell	Thapsigargin	*B. malayi*	BmK2	1 μM	48
[24]	Wang 2014	gPBMC	ConA	*H. contortus*	Hco-gal-m	10	72
[24]	Wang 2014	gPBMC	ConA	*H. contortus*	Hco-gal-m	20	72
[24]	Wang 2014	gPBMC	ConA	*H. contortus*	Hco-gal-m	40	72
[24]	Wang 2014	gPBMC	LPS	*H. contortus*	Hco-gal-m	10	72
[24]	Wang 2014	gPBMC	LPS	*H. contortus*	Hco-gal-m	20	72
[24]	Wang 2014	gPBMC	LPS	*H. contortus*	Hco-gal-m	40	72
[25]	Du 2014	mMacrophage	LPS	*T. spiralis*	rTsP53	10	12
[25]	Du 2014	mMacrophage	LPS	*T. spiralis*	rTsP53	10	6
[25]	Du 2014	mMacrophage	LPS	*T. spiralis*	rTsP53	10	12
[25]	Du 2014	mMacrophage	LPS	*T. spiralis*	rTsP53	10	24
[26]	Shen 2014	mDendritic cell	LPS	*S. japonicum*	rSj16	10	24
[27]	Figueroa-Santiago 2014	hMacrophage	LPS	*F. hepatica*	Fh12	5	24
[28]	Dlugos 2015	mSplenocyte	ConA	*T. canis*	Tc-MUC	5	24
[29]	Ferguson 2015	mMacrophage	PAM3CSK4	*S. mansoni*	omega-1	0.25	48
[30]	Wang 2015	mDendritic cell	LPS	*E. granulosus*	EgFerritin	1	20
[31]	Sanin 2015	mMacrophage	LPS	*S. mansoni*	Sm16	10	24
[31]	Sanin 2015	mMacrophage	PAM3CSK4	*S. mansoni*	Sm16	10	24
[31]	Sanin 2015	mMacrophage	Poly I:C	*S. mansoni*	Sm16	10	24
[32]	Martin 2015	mMacrophage	LPS	*F. hepatica*	Fh12	5	24
[33]	Khatri 2015	mMacrophage	LPS	*B. malayi*	rBmCys	250	72
[34]	Behrendt 2016	rMicroglia	LPS	*A. viteae*	rAVv17	250 nM	2
[34]	Behrendt 2016	rMicroglia	LPS	*A. viteae*	rAVv17	250 nM	6
[34]	Behrendt 2016	rMicroglia	LPS	*A. viteae*	rAVv17	250 nM	24
[34]	Behrendt 2016	rMicroglia	LPS	*A. viteae*	rAVv17	500 nM	24
[35]	Gadahi 2016	gPBMC	ConA	*H. contortus*	rHcES-24	5	24
[35]	Gadahi 2016	gPBMC	ConA	*H. contortus*	rHcES-24	10	24
[35]	Gadahi 2016	gPBMC	ConA	*H. contortus*	rHcES-24	20	24
[35]	Gadahi 2016	gPBMC	ConA	*H. contortus*	rHcES-24	40	24
[36]	Cao 2016	mMacrophage	LPS	*S. japonicum*	rSjHSP70	1	24
[36]	Cao 2016	mMacrophage	LPS	*S. japonicum*	rSjHSP70	10	24
[36]	Cao 2016	mMacrophage	LPS	*S. japonicum*	rSjTPx	1	24
[36]	Cao 2016	mMacrophage	LPS	*S. japonicum*	rSjTPx	10	24
[37]	Gadahi 2016	gPBMC	ConA	*H. contortus*	rHcftt-2	5	24
Continued							

References	Author	Cell type(s)	Inflamm (s)	Helminth (s)	HDIP	[HDIP] (μg/ml)	Time (hr.)
[37]	Gadahi 2016	gPBMC	ConA	*H. contortus*	rHcftt-2	10	24
[37]	Gadahi 2016	gPBMC	ConA	*H. contortus*	rHcftt-2	20	24
[37]	Gadahi 2016	gPBMC	ConA	*H. contortus*	rHcftt-2	40	24
[38]	Eason 2016	mDendritic cell	LPS	*A. viteae*	ES-62	2	18
[39]	Silva-Alvarez 2016	hMacrophage	LPS	*E. granulosus*	EgAgB	1	12
[39]	Silva-Alvarez 2016	hMacrophage	LPS	*E. granulosus*	EgAgB	10	12
[39]	Silva-Alvarez 2016	hMacrophage	LPS	*E. granulosus*	EgAgB	20	12
[39]	Silva-Alvarez 2016	hMacrophage	PMA	*E. granulosus*	EgAgB	1	12
[39]	Silva-Alvarez 2016	hMacrophage	PMA	*E. granulosus*	EgAgB	10	12
[39]	Silva-Alvarez 2016	hMacrophage	PMA	*E. granulosus*	EgAgB	20	12
[40]	Lund 2016	hMonocyte	LPS	*F. hepatica*	FhHDM-1	25 μM	12
[41]	Alvarado 2016	mMacrophage	LPS	*F. hepatica*	FhHDM-1	25 μM	3
[42]	Ehsan 2017	gPBMC	ConA	*H. contortus*	Hc-AK	5	24
[42]	Ehsan 2017	gPBMC	ConA	*H. contortus*	Hc-AK	10	24
[42]	Ehsan 2017	gPBMC	ConA	*H. contortus*	Hc-AK	20	24
[42]	Ehsan 2017	gPBMC	ConA	*H. contortus*	Hc-AK	40	24
[42]	Ehsan 2017	gPBMC	ConA	*H. contortus*	Hc-AK	80	24
[43]	Floudas 2017	mDendritic cell	LPS	*S. mansoni*	rSmCypA	n.s	24
[44]	Wang 2017	gPBMC	LPS	*H. contortus*	rHCMIF-1	10	72
[44]	Wang 2017	gPBMC	LPS	*H. contortus*	rHCMIF-1	20	72
[44]	Wang 2017	gPBMC	LPS	*H. contortus*	rHCMIF-1	40	72
[44]	Wang 2017	gPBMC	LPS	*H. contortus*	rHCMIF-1	80	72
[45]	Wang 2017	gPBMC	LPS	*H. contortus*	rHCcyst-3	10	72
[45]	Wang 2017	gPBMC	LPS	*H. contortus*	rHCcyst-3	20	72
[45]	Wang 2017	gPBMC	LPS	*H. contortus*	rHCcyst-3	40	72
[45]	Wang 2017	gPBMC	LPS	*H. contortus*	rHCcyst-3	80	72
[46]	Wang 2017	gPBMC	LPS	*H. contortus*	rHCcyst-2	10	72
[46]	Wang 2017	gPBMC	LPS	*H. contortus*	rHCcyst-2	20	72
[46]	Wang 2017	gPBMC	LPS	*H. contortus*	rHCcyst-2	40	72
[46]	Wang 2017	gPBMC	LPS	*H. contortus*	rHCcyst-2	80	72
[47]	Lumb 2017	mDendritic cell	LPS	*A. viteae*	ES-62 11a	2	18
[47]	Lumb 2017	mDendritic cell	LPS	*A. viteae*	ES-62 11e	2	18
[47]	Lumb 2017	mDendritic cell	LPS	*A. viteae*	ES-62 11i	2	18
[47]	Lumb 2017	mDendritic cell	LPS	*A. viteae*	ES-62 12b	2	18
[48]	Amdare 2017	mMacrophage	LPS	*W. bancrofti*	rWbL2	100	72
[49]	Wang 2017	hPBMC	LPS	*S. japonicum*	SJMHE1	1	24
[49]	Wang 2017	mSplenocyte	LPS	*S. japonicum*	SJMHE1	1	24
[50]	Knuhr 2018	hMonocyte	LPS	*S. mansoni*	IPSE/alpha-1	0.1	24
[51]	Ball 2018	mMast cell	LPS	*A. viteae*	ES-62	2	24
[51]	Ball 2018	mMast cell	LPS	*A. viteae*	ES-62	2	24
[52]	Zheng 2018	mMacrophage	LPS	*E. multilocularis*	emu-TegP11	100	24
[53]	Togre 2018	mMacrophage	LPS	*W. bancrofti*	rWbL2	250	42
[54]	Wang 2019	mMacrophage	LPS	*E. granulosus*	rEgTPx	10	24
[55]	Aguayo 2019	mMacrophage	LPS	*F. hepatica*	nFhGST	15	18
[55]	Aguayo 2019	mMacrophage	LPS	*F. hepatica*	nFhGST	25	18
[55]	Aguayo 2019	mMacrophage	LPS	*F. hepatica*	nFhGST	30	18
[56]	Wang 2019	gPBMC	ConA	*H. contortus*	rHCA59	10	48
[56]	Wang 2019	gPBMC	ConA	*H. contortus*	rHCA59	20	48
[56]	Wang 2019	gPBMC	ConA	*H. contortus*	rHCA59	40	48
[57]	Vacca 2020	hEK	Cytokine(s)	*H. polygyrus bakeri*	HpBARI	0.1	120
[58]	Ehsan 2020	gPBMC	ConA	*H. contortus*	rHcES-15	10	72
[58]	Ehsan 2020	gPBMC	ConA	*H. contortus*	rHcES-15	20	72
[58]	Ehsan 2020	gPBMC	ConA	*H. contortus*	rHcES-15	40	72
[58]	Ehsan 2020	gPBMC	ConA	*H. contortus*	rHcES-15	80	72
[59]	Ilgova 2020	pMacrophage	LPS	*E. nipponicum*	rEnStef	10	6
[59]	Ilgova 2020	pMacrophage	LPS	*E. nipponicum*	rEnStef	20	6
Continued							

References	Author	Cell type(s)	Inflamm (s)	Helminth (s)	HDIP	[HDIP] (μg/ml)	Time (hr.)
[60]	Kobpornchai 2020	mMacrophage	LPS	*T. spiralis*	TsCstN	10	12
[60]	Kobpornchai 2020	mMacrophage	LPS	*T. spiralis*	TsCstN	10	24
[60]	Kobpornchai 2020	mMacrophage	LPS	*T. spiralis*	TsCstN	10	12
[60]	Kobpornchai 2020	mMacrophage	LPS	*T. spiralis*	TsCstN	10	24
[61]	Shiels 2020	hMacrophage	LPS	*S. mansoni*	rSm16	5	16
[61]	Shiels 2020	hMacrophage	LPS	*S. mansoni*	rSm16	10	16
[61]	Shiels 2020	hMacrophage	LPS	*S. mansoni*	Sm16(34–117)	20	16
[61]	Shiels 2020	hMacrophage	LPS	*S. mansoni*	rSm16	25	16
[61]	Shiels 2020	hMacrophage	LPS	*S. mansoni*	rSm16	50	16
[62]	Wang 2020	gPBMC	ConA	*H. contortus*	rHCRD	10	72
[62]	Wang 2020	gPBMC	ConA	*H. contortus*	rHCRD	20	72
[62]	Wang 2020	gPBMC	ConA	*H. contortus*	rHCRD	40	72
[63]	Wang 2020	gPBMC	ConA	*H. contortus*	rHCPTPA	10	72
[63]	Wang 2020	gPBMC	ConA	*H. contortus*	rHCPTPA	20	72
[63]	Wang 2020	gPBMC	ConA	*H. contortus*	rHCPTPA	40	72
[64]	Wang 2020	gPBMC	ConA	*H. contortus*	rHCETFα	10	72
[64]	Wang 2020	gPBMC	ConA	*H. contortus*	rHCETFα	20	72
[64]	Wang 2020	gPBMC	ConA	*H. contortus*	rHCETFα	40	72
[65]	Naqvi 2020	gPBMC	PMA	*H. contortus*	rHc-GDC	10	48
[65]	Naqvi 2020	gPBMC	PMA	*H. contortus*	rHc-GDC	20	48
[65]	Naqvi 2020	gPBMC	PMA	*H. contortus*	rHc-GDC	40	48
[65]	Naqvi 2020	gPBMC	PMA	*H. contortus*	rHc-GDC	80	48
[66]	Lu 2020	gPBMC	ConA	*H. contortus*	rHcADRM1	5	24
[66]	Lu 2020	gPBMC	ConA	*H. contortus*	rHcADRM1	10	24
[66]	Lu 2020	gPBMC	ConA	*H. contortus*	rHcADRM1	20	24
[66]	Lu 2020	gPBMC	ConA	*H. contortus*	rHcADRM1	40	24
[67]	Lu 2020	gPBMC	ConA	*H. contortus*	rHcABHD	10	24
[67]	Lu 2020	gPBMC	ConA	*H. contortus*	rHcABHD	20	24
[67]	Lu 2020	gPBMC	ConA	*H. contortus*	rHcABHD	40	24
[67]	Lu 2020	gPBMC	ConA	*H. contortus*	rHcABHD	80	24
[68]	Montero 2020	mDendritic cell	LPS	*T. crassiceps*	GK-1	10	24
[68]	Montero 2020	mDendritic cell	LPS	*T. crassiceps*	GK-1	100	24
[69]	Buitrago 2021	hMacrophage	LPS	*N. americanus*	Na-AIP-1	100	24
[70]	Ehsan 2021	gPBMC	ConA	*F. gigantica*	rFg-CaBP4	5	26
[70]	Ehsan 2021	gPBMC	ConA	*F. gigantica*	rFg-CaBP4	10	26
[70]	Ehsan 2021	gPBMC	ConA	*F. gigantica*	rFg-CaBP4	20	26
[70]	Ehsan 2021	gPBMC	ConA	*F. gigantica*	rFg-CaBP4	40	26
[71]	Xie 2021	mMacrophage	LPS	*S. japonicum*	rSj-Cys	2	24
[72]	Corbet 2021	mFibroblast	Cytokine(s)	*A. viteae*	ES-62	2	24
[72]	Corbet 2021	mFibroblast	Cytokine(s)	*A. viteae*	ES-62	2	24
[72]	Corbet 2021	mFibroblast	LPS	*A. viteae*	ES-62	2	24
[72]	Corbet 2021	mFibroblast	PAM3CSK4	*A. viteae*	ES-62	2	24
[73]	Smallwood 2021	hPBMC	PMA	*A. caninum*	Acan1	0.001	24
[73]	Smallwood 2021	hPBMC	PMA	*A. caninum*	Acan1	0.01	24
[73]	Smallwood 2021	hPBMC	PMA	*A. caninum*	Acan1	0.5	24
[73]	Smallwood 2021	hPBMC	PMA	*A. caninum*	Acan1	1	24
[73]	Smallwood 2021	hPBMC	PMA	*A. caninum*	Acan1	5	24
[73]	Smallwood 2021	hPBMC	PMA	*A. caninum*	Acan1	10	24
[73]	Smallwood 2021	hPBMC	PMA	*A. caninum*	Acan1	20	24
[73]	Smallwood 2021	hPBMC	PMA	*A. caninum*	Acan1	50	24
[73]	Smallwood 2021	hPBMC	PMA	*N. americanus*	Nak1	0.001	24
[73]	Smallwood 2021	hPBMC	PMA	*N. americanus*	Nak1	0.01	24
[73]	Smallwood 2021	hPBMC	PMA	*N. americanus*	Nak1	0.5	24
[73]	Smallwood 2021	hPBMC	PMA	*N. americanus*	Nak1	1	24
[73]	Smallwood 2021	hPBMC	PMA	*N. americanus*	Nak1	5	24
[73]	Smallwood 2021	hPBMC	PMA	*N. americanus*	Nak1	10	24

Continued

References	Author	Cell type(s)	Inflamm (s)	Helminth (s)	HDIP	[HDIP] (μg/ml)	Time (hr.)
[73]	Smallwood 2021	hPBMC	PMA	*N. americanus*	Nak1	20	24
[73]	Smallwood 2021	hPBMC	PMA	*N. americanus*	Nak1	50	24
[74]	Ryan 2022	hT cell	Anti-CD3 & Anti-CD28	*A. caninum*	ANCCAN_07727	50	24
[74]	Ryan 2022	hT cell	Anti-CD3 & Anti-CD29	*A. caninum*	Ac-FAR-2	10	24
[74]	Ryan 2022	hT cell	Anti-CD3 & Anti-CD30	*A. caninum*	ANCCAN_07322	50	24
[74]	Ryan 2022	hT cell	Anti-CD3 & Anti-CD31	*A. caninum*	ANCCAN_22177	50	24
[74]	Ryan 2022	hT cell	Anti-CD3 & Anti-CD32	*A. caninum*	ANCCAN_08034	50	24
[75]	Kobpornchai 2022	hNeutrophil	fMLP	*T. spiralis*	rTsSERP1	10	4
[75]	Kobpornchai 2022	hNeutrophil	fMLP	*T. spiralis*	rTsSERP1	10	4
[76]	Wang 2022	mMacrophage	LPS	*F. hepatica*	rGSTO2	10	24
[77]	Loghry 2022	hMacrophage	Cytokine(s)	*B. malayi*	Bma-LEC-1	0.5 μM	72
[77]	Loghry 2022	hMacrophage	Cytokine(s)	*B. malayi*	Bma-LEC-2	0.5 μM	72
[78]	Zhang 2022	mMacrophage	LPS	*F. hepatica*	rFhCystatin	1	24
[78]	Zhang 2022	mMacrophage	LPS	*F. hepatica*	rFhCystatin	2.5	24
[78]	Zhang 2022	mMacrophage	LPS	*F. hepatica*	rFhCystatin	5	24
[79]	Li 2022	mMacrophage	LPS	*T. spiralis*	rTs-Cys	0.5	24
[80]	Zawistowska 2022	hDendritic cell	LPS	*F. hepatica*	FhCL5	25	48
[80]	Zawistowska 2022	hDendritic cell	LPS	*F. hepatica*	fhFABP1	25	48
[80]	Zawistowska 2022	hDendritic cell	LPS	*F. hepatica*	FhFABP5	25	48
[81]	Ruiz-Jiménez 2022	mDendritic cell	LPS	*F. hepatica*	Fh12	2.5	24
[82]	Stachyra 2023	mSplenocyte	LPS	*T. britovi*	CLP	10	24
[82]	Stachyra 2023	mSplenocyte	LPS	*T. britovi*	CLP	10	48
[82]	Stachyra 2023	mSplenocyte	LPS	*T. britovi*	CLP	10	72
[83]	Xifeng 2023	mMacrophage	LPS	*F. hepatica*	rGSTO1	10	24
[84]	Chantree 2023	mMacrophage	LPS	*F. gigantica*	rFgCyst	5	24
[84]	Chantree 2023	mMacrophage	LPS	*F. gigantica*	rFgCyst	10	24
[84]	Chantree 2023	mMacrophage	LPS	*F. gigantica*	rFgCyst	20	24
[84]	Chantree 2023	hMacrophage	LPS	*F. gigantica*	rFgCyst	5	24
[84]	Chantree 2023	hMacrophage	LPS	*F. gigantica*	rFgCyst	10	24
[84]	Chantree 2023	hMacrophage	LPS	*F. gigantica*	rFgCyst	20	24
[84]	Chantree 2023	mMacrophage	LPS	*F. gigantica*	rFgCyst	5	24
[84]	Chantree 2023	mMacrophage	LPS	*F. gigantica*	rFgCyst	10	24
[84]	Chantree 2023	mMacrophage	LPS	*F. gigantica*	rFgCyst	20	24
[84]	Chantree 2023	hMacrophage	LPS	*F. gigantica*	rFgCyst	5	24
[84]	Chantree 2023	hMacrophage	LPS	*F. gigantica*	rFgCyst	10	24
[84]	Chantree 2023	hMacrophage	LPS	*F. gigantica*	rFgCyst	20	24
[85]	Quinteros 2023	mMacrophage	LPS	*F. hepatica*	FhHDM-1	2.5 μM	24
[85]	Quinteros 2023	mMacrophage	LPS	*F. hepatica*	FhHDM-1	10 μM	24
[85]	Quinteros 2023	mMacrophage	LPS	*F. hepatica*	FhHDM-1	15 μM	24
[86]	Colomb 2024	mEpithelial	Freeze–thaw	*H. polygyrus bakeri*	HpARI2	10	48
[86]	Colomb 2024	mEpithelial	Freeze–thaw	*H. polygyrus bakeri*	HpARI3	10	48
[87]	Yang 2024	mMacrophage	LPS	*C. pisiformis*	rCpStefin	5	24
[87]	Yang 2024	mMacrophage	LPS	*C. pisiformis*	rCpStefin	10	24
[87]	Yang 2024	mMacrophage	LPS	*C. pisiformis*	rCpStefin	20	24
[88]	Ehsan 2024	gPBMC	ConA	*F. gigantica*	Fg-LGMN-1	5	2
[88]	Ehsan 2024	gPBMC	ConA	*F. gigantica*	Fg-LGMN-1	10	2
[88]	Ehsan 2024	gPBMC	ConA	*F. gigantica*	Fg-LGMN-1	20	2
[88]	Ehsan 2024	gPBMC	ConA	*F. gigantica*	Fg-LGMN-1	40	2
[89]	Folle 2024	mMacrophage	LPS	*E. granulosus*	EgAgB	1	24
[89]	Folle 2024	mMacrophage	LPS	*E. granulosus*	EgAgB	10	24
[89]	Folle 2024	hMacrophage	LPS	*E. granulosus*	EgAgB	1	24
[89]	Folle 2024	hMacrophage	LPS	*E. granulosus*	EgAgB	10	24
[89]	Folle 2024	mMacrophage	LPS	*E. granulosus*	rEgAgB8/1	1	24
[89]	Folle 2024	mMacrophage	LPS	*E. granulosus*	rEgAgB8/1	10	24
[89]	Folle 2024	hMacrophage	LPS	*E. granulosus*	rEgAgB8/1	1	24
[89]	Folle 2024	hMacrophage	LPS	*E. granulosus*	rEgAgB8/1	10	24

Continued

References	Author	Cell type(s)	Inflamm (s)	Helminth (s)	HDIP	[HDIP] (μg/ml)	Time (hr.)
[90]	Gong 2024	mMacrophage	LPS	*F. hepatica*	CL7	15	12
[90]	Gong 2024	mMacrophage	LPS	*F. hepatica*	CL7	15	12
[91]	Li 2024	mMacrophage	LPS & IFNγ	*E. multilocularis*	Emu-serpin	50,000	24
[92]	Lalor 2025	mMacrophage	LPS	*F. hepatica*	FhHDM-1.c2	20	16
[92]	Lalor 2025	hMacrophage	LPS	*F. hepatica*	FhHDM-1.c2	20	16

References	Method	IL12 (%)	IL1β (%)	IL6 (%)	TNFα (%)	IL2 (%)	IFNγ (%)	IL17 (%)	IL4 (%)	TGFβ (%)	IL10 (%)
[14]	El	−66					−29				114
[15]	El	−95			−73						
[15]	El	−95			−63						
[15]	El	−93			−51						
[16]	El						170				−17
[17]	El			−45	−39						
[17]	El			−57	−63		−48				
[18]	El	−60									
[18]	El	−79									
[18]	El	−32									
[19]	El	−87		−60	−71						−96
[20]	El						−58		−26		
[21]	El			−95							
[21]	El			−99							−75
[21]	El			−95							
[21]	El			−97							−53
[22]	El						24		5	12	Excl
[23]	El						−6				
[23]	El						−82				
[23]	El						−34				
[23]	El						−17				
[23]	El						−33				
[23]	El						−79				
[24]	El			−46	−31						5
[24]	El			−80	−63						−54
[24]	El			−90	−65						−92
[24]	El			−3	−54						20
[24]	El			0	−59						99
[24]	El			−8	−80						120
[25]	qP	−70									
[25]	El			−29	−37					48	39
[25]	El			−22	−24					40	31
[25]	El			−20	−21					45	24
[26]	qP										Excl
[27]	qP	−94	−46		−77						215
[28]	El			84	18		93	−22	−90	33	−48
[29]	El		Excl								
[30]	El	Excl		47	Excl						293
[31]	El	−98									−63
[31]	El	36									34
[31]	El	−86									−62
[32]	qP	Excl	−86	−48	−51						
[33]	qP			−87	−74					93	
[34]	qP										62
[34]	qP		2	30	1						4
[34]	qP		−34	−20	−38						36
[34]	qP		−30	−39	−16						
[35]	El						−4	35	−2		58
[35]	El						−10	167	3		73
[35]	El						−21	141	11		150

Continued

References	Method	IL12 (%)	IL1β (%)	IL6 (%)	TNFα (%)	IL2 (%)	IFNγ (%)	IL17 (%)	IL4 (%)	TGFβ (%)	IL10 (%)
[35]	El						− 38	163	17		171
[36]	qP		− 86	− 67	− 66						
[36]	qP		− 94	− 87	− 75						
[36]	qP		− 40	− 58	− 52						
[36]	qP		− 71	− 76	− 65						
[37]	El						72	19	− 5		37
[37]	El						108	77	− 12		30
[37]	El						122	137	− 38		69
[37]	El						133	221	− 40		73
[38]	El	− 38		− 30	− 49						
[39]	El		− 38		− 71						− 3
[39]	El		− 70		− 81						30
[39]	El		− 91								6
[39]	El		− 4		7						− 3
[39]	El		− 48		− 65						30
[39]	El		− 67		− 70						6
[40]	El			− 90	− 90						
[41]	El		38								
[42]	El						13	15	38	− 5	16
[42]	El						18	28	39	− 19	21
[42]	El						31	34	62	− 20	37
[42]	El						36	42	59	− 21	46
[42]	El						39	47	52	− 28	71
[43]	El	− 16			− 17						
[44]	El	− 6	− 21		− 8					10	16
[44]	El	− 12	− 32		− 24					31	24
[44]	El	− 21	− 46		− 37					48	39
[44]	El	− 30	− 65		− 45					63	63
[45]	El	− 5	− 15		− 10					24	16
[45]	El	− 11	− 34		− 17					51	23
[45]	El	− 18	− 46		− 34					69	37
[45]	El	− 23	− 58		− 46					84	62
[46]	El	− 3	− 17		− 7					3	18
[46]	El	− 10	− 28		− 15					3	23
[46]	El	− 16	− 41		− 33					0	39
[46]	El	− 21	− 55		− 38					2	61
[47]	El	− 100		− 79	− 67						
[47]	El	− 100		− 49	− 61						
[47]	El	− 100		− 71	− 44						
[47]	El	− 100		− 77	− 68						
[48]	El				− 61		− 55				92
[49]	El		− 11	− 34	− 40						
[49]	El			− 22		− 22			− 57		
[50]	El		− 13	22							
[51]	El			− 13							
[51]	El			− 10							
[52]	qP	− 44	− 38	42	− 25				119		21
[53]	qP			− 80	− 91					219	
[54]	qP				− 58						Excl
[55]	qP		− 99		− 85						
[55]	qP		− 98		− 88						
[55]	qP		− 98		− 83						
[56]	qP					60	69	43	40	34	97
[56]	qP					54	106	146	169	37	163
[56]	qP					49	146	Excl	134	54	Excl
[57]	El			− 72							
[58]	El						− 21	− 56	− 42	− 22	− 39

References	Method	IL12 (%)	IL1β (%)	IL6 (%)	TNFα (%)	IL2 (%)	IFNγ (%)	IL17 (%)	IL4 (%)	TGFβ (%)	IL10 (%)
[58]	El						−27	−49	−31	−28	−32
[58]	El						−32	−33	−16	−33	−24
[58]	El						−36	−20	−9	−39	−10
[59]	qP				−24						−26
[59]	qP				−33						−52
[60]	qP		−65		−75		−94				
[60]	qP		−80		−98		−79				
[60]	qP				−51		−79				
[60]	qP				−84		−79				
[61]	El			−2	−14						
[61]	El			−8	−35						
[61]	El			−49	−85						
[61]	El			−17	−51						
[61]	El			−32	−69						
[62]	El				2	−2	−24	−2	1	16	75
[62]	El				−52	−4	−44	2	−4	19	136
[62]	El				−41	0	−44	1	−1	74	261
[63]	El				−1	−42	4	−3	22	5	23
[63]	El				−1	−40	−26	1	54	14	143
[63]	El				−1	−46	−52	−3	31	11	159
[64]	El				−28	−25	1	−3	−16	97	−3
[64]	El				−55	−40	−3	−40	−21	99	1
[64]	El				−65	−41	1	−62	−62	108	1
[65]	qP						11		5		5
[65]	qP						22		83		11
[65]	qP						11		180		11
[65]	qP						9		159		14
[66]	El					14	−7	7	−9	5	−6
[66]	El					13	−15	13	−18	−3	−15
[66]	El					9	−15	0	−23	1	−19
[66]	El					14	−19	1	−23	−10	−23
[67]	El					5	−3	−4	−10	−11	−7
[67]	El					−13	−12	5	−26	−15	13
[67]	El					−15	−15	14	−21	−27	14
[67]	El					−2	−10	−11	−17	−28	28
[68]	El	−100		−1	−43						
[68]	El	−67		−14	−43						
[69]	El				−31						
[70]	qP				1	−4	12		200	15	−16
[70]	qP				7	−2	3		204	15	−58
[70]	qP				−1	32	161		Excl	Excl	−72
[70]	qP				7	89	136		236	285	−71
[71]	El			−17			−46			122	46
[72]	El			−34							
[72]	El			−13							
[72]	El			31							
[72]	El			−5							
[73]	El				−18	−37					
[73]	El				−5	−23					
[73]	El				−16	−31					
[73]	El				−29	−43					
[73]	El				−28	−36					
[73]	El				−33	−51					
[73]	El				−44	−68					
[73]	El				−76	−95					
[73]	El				−8	−26					
[73]	El				−34	−42					

References	Method	IL12 (%)	IL1β (%)	IL6 (%)	TNFα (%)	IL2 (%)	IFNγ (%)	IL17 (%)	IL4 (%)	TGFβ (%)	IL10 (%)
[73]	El				− 21	− 41					
[73]	El				− 18	− 38					
[73]	El				− 34	− 46					
[73]	El				− 21	− 50					
[73]	El				− 12	− 54					
[73]	El				− 15	− 65					
[74]	El				− 97		− 25	− 31			
[74]	El				− 53		− 7	− 8			
[74]	El				− 48		− 21	− 28			
[74]	El				− 19		4	24			
[74]	El				− 55		− 30	− 7			
[75]	qP		− 58	− 72	− 72		− 71				
[75]	El		− 55				− 61				
[76]	qP	− 60	− 85	− 74	− 59		− 40			− 10	− 4
[77]	El										− 2
[77]	El										43
[78]	El			− 23	− 18					− 47	− 9
[78]	El			− 26	− 18					− 30	8
[78]	El			− 37	− 26					0	43
[79]	El			− 40	− 32						87
[80]	El	70		35			26		− 2		52
[80]	El	− 33		− 55			− 22		49		143
[80]	El	38		− 18			9		20		46
[81]	El	− 37		− 29							145
[82]	El			− 24	− 11						3
[82]	El			− 21	− 5						− 11
[82]	El			− 28	− 16						− 21
[83]	El		− 57	− 43	− 58						− 7
[84]	qP		− 25	− 54	− 22						
[84]	qP		− 51	− 67	− 47						
[84]	qP		− 70	− 76	− 77						
[84]	qP		− 22	− 24	− 25						
[84]	qP		− 59	− 67	− 58						
[84]	qP		− 75	− 80	− 82						
[84]	WB		− 10	− 18	− 19						
[84]	WB		− 24	− 37	− 34						
[84]	WB		− 42	− 43	− 43						
[84]	WB		− 8	− 16	− 7						
[84]	WB		− 24	− 28	− 15						
[84]	WB		− 36	− 44	− 35						
[85]	El			− 92	− 11						
[85]	El				− 24						
[85]	El				− 40						
[86]	El										
[86]	El										
[87]	El		− 11	− 10	− 2						
[87]	El		− 16	− 14	− 8						
[87]	El		− 27	− 20	− 15						
[88]	qP					52		19	− 40		− 24
[88]	qP					67		19	− 48		1
[88]	qP					80		47	− 82		18
[88]	qP					132		94	− 82		66
[89]	El	− 84		− 95							
[89]	El	− 97		− 99							
[89]	El		− 49	− 75							
[89]	El		− 80	− 94							
[89]	El	− 68		− 82							

References	Method	IL12 (%)	IL1β (%)	IL6 (%)	TNFα (%)	IL2 (%)	IFNγ (%)	IL17 (%)	IL4 (%)	TGFβ (%)	IL10 (%)
[89]	El	− 89		− 98							
[89]	El		− 30	− 66							
[89]	El		− 56	− 85							
[90]	qP		− 73	− 68	− 68						
[90]	qP		− 75	− 61	− 61						
[91]	qP		− 88		− 86					162	243
[92]	El				− 61						
[92]	El				− 85						

Table 1. Studies and individual records included in this review. A total of 79 articles were included in this review from which 229 separate records were identified. For each of these records, the percent change in cytokine levels is shown. The lowercase letter before each cell types denotes the species of origin: human (h), mouse (m), goat (g), rat (r), pig (p). Method refers to the method used for cytokine analysis: ELISA (El); qPCR (qP); WB (Western immunoblotting). See Supplementary Excel file for more details and specific values. ConA, concanavalin A; EK, embryonic kidney; fMLP, N-Formylmethionine-leucyl-phenylalanine; Inflamm(s), inflammagen(s); LPS, lipopolysaccharide; PBMC, peripheral blood mononuclear cell; PMA, phorbol myristate acetate. Excl, values excluded as statistical outliers. Some cytokines were measured infrequently (< 5 records) and these have been omitted from this table (these include: IL-5, IL-8, IL-9, IL-13 and INFβ).

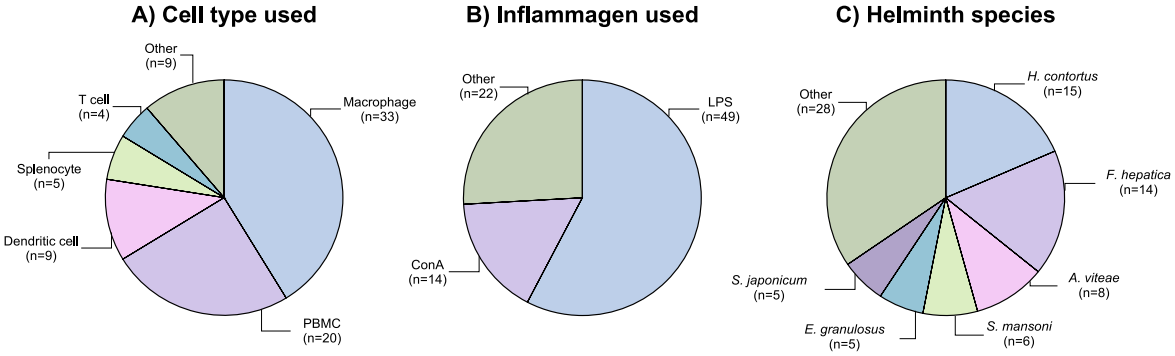


Fig. 2. General study characteristics. A total of 79 articles were included in this review and a summary of the key characteristics of these articles is depicted in these pie charts. These show the proportions of these studies using different (**A**) cell types, (**B**) inflammagens and (**C**) helminth species. LPS, lipopolysaccharide; ConA, concanavalin A; PBMC, peripheral blood mononuclear cell.

Results

General study characteristics

Seventy-nine articles were included in this review in which HDIPs were assessed for their immunomodulatory effects in in vitro cellular models of inflammation (Table 1 and Supplementary Excel file). We found that most published studies used macrophages, peripheral blood mononuclear cells (PBMCs) or dendritic cells as the target immune cell (Fig. 2A), and LPS or Concanavalin A to elicit inflammatory responses (Fig. 2B). Although 20 different helminth species tested in these studies, the most widely used were the nematodes, *Haemonchus contortus* and *Acanthocheilonema viteae,* the trematodes, *Fasciola hepatica*, *Schistosoma mansoni* and *Schistosoma japonicum*, and the cestode, *Echinococcus granuloses* (together tested in 65% of studies) (Fig. 2C). From the collective helminth species, > 60 different sequenced HDIPs were tested (Table 1 and Supplementary Excel file), and although there was no widely used HDIP, ES-62 (a phosphorylcholine-containing glycoprotein secreted by *A. viteae)* was used most frequently (n = 7 articles).

Effect of HDIPs on cytokines

From the 79 articles included in this review, 229 separate records were identified in which HDIPs were assessed for their effect on cytokine levels in cellular models of inflammation. Taking all this data together, the effect of the HDIPs on the most widely assessed cytokines was first examined (Fig. 3). This revealed that levels of the pro-inflammatory cytokines, IL-12, IL-1β, IL-6 and TNFα were all significantly reduced by the HDIPs (IL-12: $t_{(42)} = 7.41$, $P < 0.0001$; IL-1β:$t_{(61)} = 12.73$, $P < 0.0001$; IL-6: $t_{(92)} = 10.55$, $P < 0.0001$; TNFα:$t_{(138)} = 17.66$, $P < 0.0001$). In contrast, levels of the anti-inflammatory cytokines, IL-10, TGFβ and IL-4 were significantly increased (IL-10: ($t_{(109)} = 4.80$, $P < 0.0001$; TGFβ:$t_{(56)} = 3.54$, $P < 0.001$; IL4: $t_{(55)} = 2.01$, $P < 0.05$). The HDIPs also increased levels of the pro-inflammatory cytokine IL-17 ($t_{(45)} = 2.78$, $P < 0.01$), but neither IL-2 nor IFNγ were significantly changed (from zero) overall.

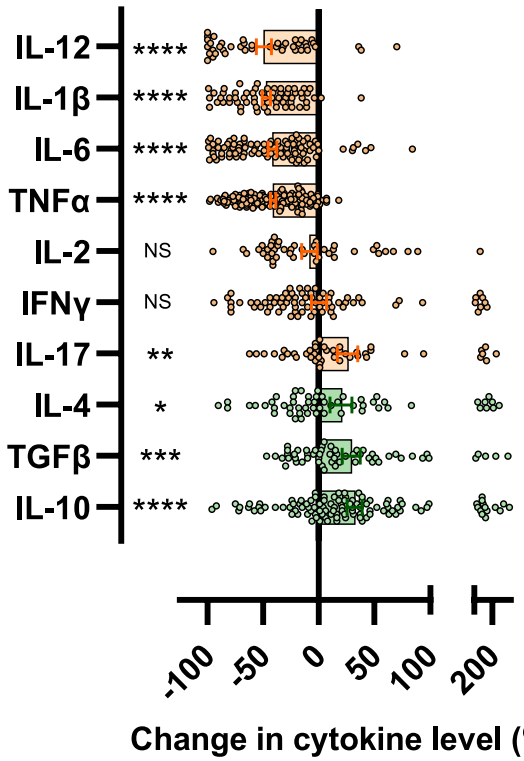


Fig. 3. Effect of HDIPs on cytokines overall. The effect of the HDIPs on the most widely assessed cytokines. Each data point represents a specific record extracted from Table 1/Supplementary Excel file, and the mean ± sem is also shown. Data were analysed by one-sample test with the hypothesised population mean set to zero. ****$P<0.0001$, ***$P<0.001$, **$P<0.01$ and *$P<0.05$. NS: not-significantly different to zero.

Effect of cell type and inflammagen on efficacy of HDIPs

The effects of main cell type and inflammagen on the ability of the HDIPs to modify cytokine levels was then assessed (Fig. 4). This highlighted that cell type (Fig. 4A) but not inflammagen (Fig. 4C) had a significant effect on the ability of the HDIPs to reduce pro-inflammatory cytokine expression. Specifically, the HDIPs reduced IL-12 and TNFα significantly more in macrophages than PBMCs (Fig. 4A; Cell type: $F_{(1,247)}=32.78$; $P<0.0001$). In contrast, neither cell type (Fig. 4B) nor inflammagen (Fig. 4D) affected the ability of the HDIPs to increase anti-inflammatory cytokine levels.

Effects of HDIPs from specific species on cytokines

The effects of the HDIPs from the most widely used species were then assessed in terms of their effect on the most affected pro-inflammatory (IL-12, IL-1β, IL-6 and TNFα) and anti-inflammatory (IL-10, TGFβ and IL-4) cytokines (Fig. 5). This demonstrate that HDIPs from all the widely used species significantly reduced pro-inflammatory cytokine levels (Fig. 5A; *Echinococcus granuloses:* $t_{(31)}=11.30$, $P<0.0001$; *Schistosoma japonicum:* $t_{(16)}=9.18$, $P<0.0001$; *Fasciola hepatica:* $t_{(47)}=9.03$, $P<0.0001$; *Acanthocheilonema viteae:* $t_{(42)}=9.20$, $P<0.0001$; *Schistosoma mansoni*: $t_{(20)}=7.41$, $P<0.001$; *Haemonchus contortus:* $t_{(56)}=10.05$, $P<0.0001$). There was less data available for the anti-inflammatory cytokines, but it was evident that HDIPs from *Haemonchus contortus* were capable of both reducing pro-inflammatory cytokine levels, as well as significantly increasing anti-inflammatory cytokine levels (Fig. 5B; *Haemonchus contortus:* $t_{(139)}=5.61$, $P<0.0001$).

Effects of HDIPs from specific species on specific cytokines

This data were then further subdivided to determine the effects of the HDIPs from the most widely used species on the most affected pro-inflammatory cytokines individually (Fig. 6). This demonstrated that HDIPs from *Echinococcus granuloses* significantly reduced levels of all of the most affected pro-inflammatory cytokines (Fig. 6: IL-12*:* $t_{(4)}=17.84$, $P<0.0001$; IL-1β*:* $t_{(9)}=6.60$, $P<0.0001$; IL-6*:* $t_{(9)}=5.14$, $P<0.001$; TNFα*:* $t_{(6)}=5.21$, $P<0.01$). HDIPs from the other species also significantly reduced levels of most of the pro-inflammatory cytokines (statistical outcomes in Fig. 6).

Similarly, the data were also subdivided to determine the effects of the HDIPs from the most widely used species on the most affected anti-inflammatory cytokines individually (Fig. 7). Although there was less data available for the anti-inflammatory cytokines, there were sufficient data points for *Haemonchus contortus* to note that HDIPs from this species significantly increase IL-10 and (to a lesser extent) TGFβ levels, but do not significantly increase IL-4 levels (Fig. 7: IL-10*:* $t_{(57)}=4.91$, $P<0.0001$; TGFβ*:* $t_{(40)}=2.58$, $P<0.05$; IL-4*:* $t_{(40)}=1.94$, $P>0.05$).

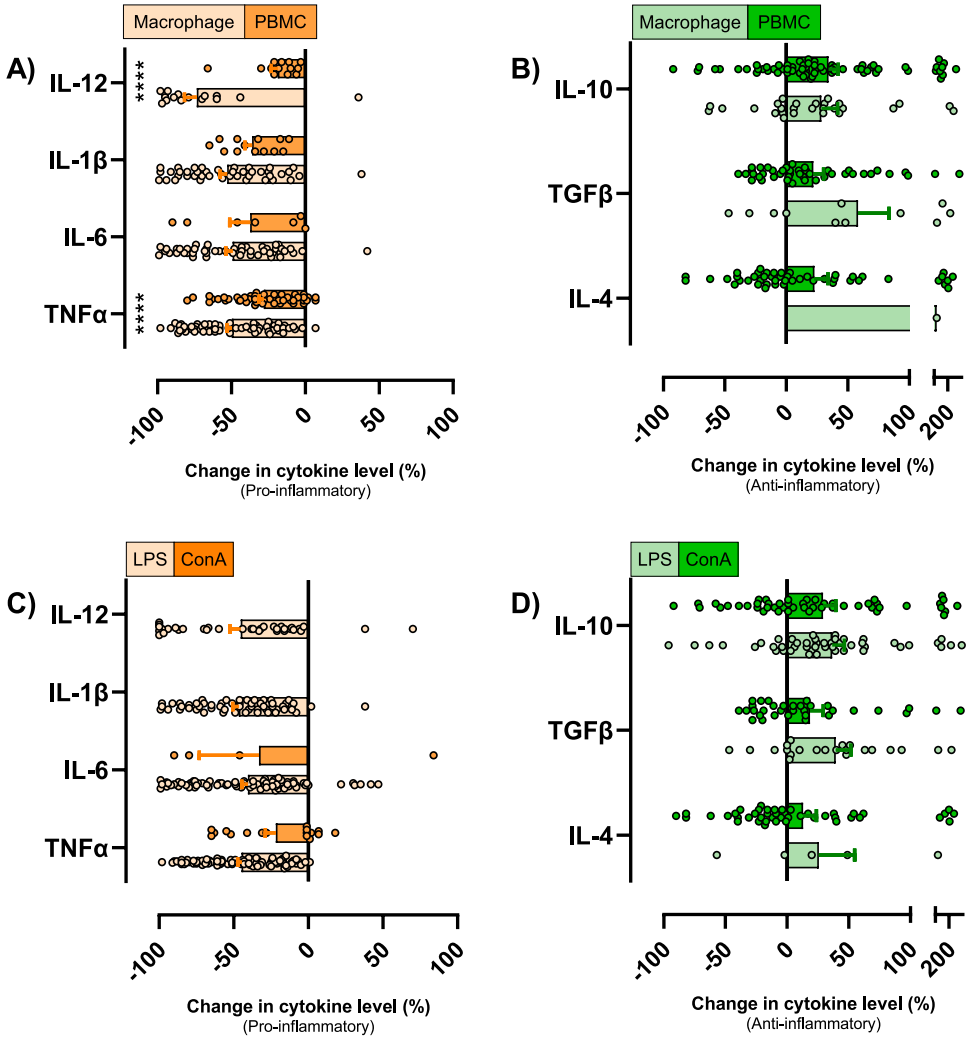


Fig. 4. Effect of cell type and inflammagen on efficacy of HDIPs. The effect of (**A**) & (**B**) cell type and (**C**) & (**D**) inflammagen on pro-inflammatory and anti-inflammatory cytokine levels. Each data point represents a specific record extracted from Table 1/Supplementary Excel file, and the mean ± sem is also shown. Data were analyzed by two-way ANOVA with *post-hoc* Bonferroni. ****$P < 0.0001$ Macrophage vs. PBMC.

Effects of mechanistic classes of HDIPs on cytokines

The effect of HDIPs was also assessed based on their known functional classification (Fig. 8). This demonstrated that HDIPs that function as cysteine proteases were capable of both reducing pro-inflammatory ($t_{(99)} = 13.58$, $P < 0.0001$) and increasing anti-inflammatory ($t_{(37)} = 3.79$, $P < 0.001$) cytokine levels. In contrast, the other classes assessed (cathelicidin-like HDIPs, ShK-related HDIPs, fatty acid binding HDIPs, glutathione transferase HDIPs, galectin HDIPs and thioredoxin peroxidase HDIPs) were also capable of reducing pro-inflammatory cytokine levels but were less effective at increasing anti-inflammatory cytokine levels (or this was not assessed).

Effects of cell species on change in cytokine levels by HDIPs

Another consideration was whether or not the species from which the cells were derived had any effect on change in cytokine levels induced by the HDIPs. Sufficient records allowed for this comparison for selected pro-inflammatory cytokines in mouse versus human macrophages (Fig. 9A) and goat versus human PBMCs only (Fig. 9B). This highlighted that HDIPs reduced pro-inflammatory cytokine levels to the same extent in macrophages derived from mice and humans. In contrast, in PBMCs, there was significant difference in the ability of the HDIPs to reduce pro-inflammatory cytokine levels (Fig. 9B; Species x Cytokine: $F_{(1,85)} = 20.84$; $P < 0.0001$). Specifically, while HDIP-induced reductions in TNFα levels were not affected by species, the HDIPs reduced IL-2 levels in human PBMCs but not in goat PBMCs.

Effects of specific HDIPs on cytokines

Finally, the data were plotted by individual HDIP for the most widely assessed pro-inflammatory and anti-inflammatory cytokines (Fig. 10). The overwhelming trend for a reduction in proinflammatory cytokine levels (Fig. 10A) and an increase in anti-inflammatory cytokine levels (Fig. 10B) across HDIPs is clear.

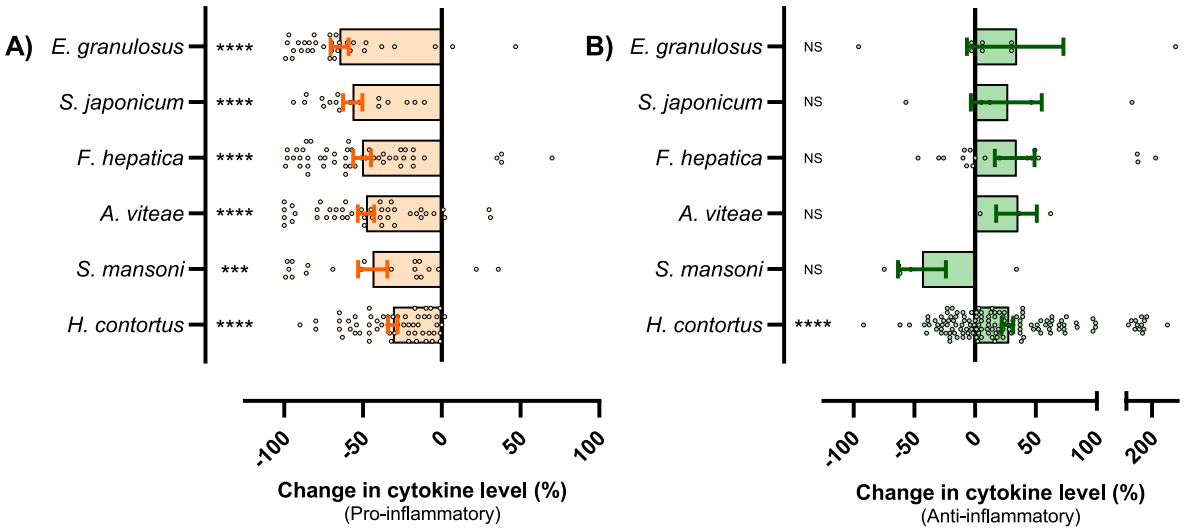


Fig. 5. Effect of HDIPs from specific species on cytokine levels. The effect of the HDIPs from the most widely used species on (**A**) pro-inflammatory (IL-12, IL-1β, IL-6 and TNFα) and (**B**) anti-inflammatory (IL-10, TGFβ and IL-4) cytokine levels. Each data point represents a specific record extracted from Table 1/Supplementary Excel file, and the mean ± sem is also shown. Data were analysed by one-sample test with the hypothesised population mean set to zero. ****$P < 0.0001$ and ***$P < 0.001$. NS, not-significantly different to zero.

Discussion

Secretory products of helminths have become a topic of interest in the last 20 years due to their immunomodulatory properties, leading researchers to investigate HDIPs as therapeutic molecules for different immune and inflammatory conditions[1,4,11]. Preclinical studies in both cellular and animal models have assessed these immunomodulatory properties using various helminth species, HDIPs, inflammagens, disease models, experimental parameters and measured outcomes in terms of functionality of immune cells and their secretome. In this review, we focussed on consolidating the studies in cellular models with a focus on the effect of HDIPs on cytokine levels. Using a systematic approach, we identified 79 articles in which > 60 HDIPs from 20 helminth species were assessed largely in LPS or Concanavalin A stimulated macrophages, peripheral blood mononuclear cells or dendritic cells. Regardless of inflammagen, cell type or species, the overwhelming effect of the HDIPs was a reduction in expression or production of pro-inflammatory cytokines such as IL-12, IL-1β, IL-6 and TNF, and an increase in anti-inflammatory cytokines such as IL-10, TGFβ and IL-4. Note that although IL-4 is a pleiotropic cytokine which has critical pro-inflammatory effects via driving Th2 responses (including to combat helminth infections[9]), it was included in this analysis with IL-10 and TGFβ because of its recognised anti-inflammatory effects[93]. Because of their profound effect on cytokine levels, this systematic review adds to the growing body of literature that supports the exploration of helminth secretory products as potential therapeutics in pathological conditions driven by overactive immune and inflammatory responses.

Although this review identified > 60 HDIPs from 20 helminth species, the most widely used species for derivation of HDIPs were the nematodes, *Haemonchus contortus* and *Acanthocheilonema viteae,* the trematodes, *Fasciola hepatica*, *Schistosoma mansoni* and *Schistosoma japonicum*, and the cestode, *Echinococcus granuloses*. These have adapted to suppress their host's immune system, allowing them to be tolerated by the host for significant periods of time. For example, the blood flukes, *Schistosoma mansoni* and *Schistosoma japonicum* have very long infection periods and can persist in humans for decades[94], whereas, in contrast, infections by the liver fluke, *Fasciola hepatica*[95], or the blood-sucking roundworm, *Haemonchus contortus*[96], are typically shorter, lasting months or years. Regardless of the duration of the infective period, these endoparasites have evolved multiple mechanisms through which they can evade, modulate and suppress the immune system of the host species, including the secretion of immunomodulatory HDIPs.

This study review revealed that > 60 different HDIPs have been assessed for their effect on cytokine responses in immune cells. The most common mechanistic class of the molecules assessed was cysteine protease activity which is associated with HDIPs from many species[97–99]. Helminths, along with many other pathogens, have evolved to secrete cysteine proteases that facilitate invasion, infection and immune suppression of the host. These have various effects ranging from degradation (of extracellular matrix components, for example) of proteins to facilitate helminth invasion, to degradation of many proteins involved in the immune response. These cysteine protease HDIPs can cleave the hinge region in IgG antibodies, cleave and inactivate pro-inflammatory cytokines, and degrade and inactivate pathogen-detecting Toll-like receptors among many other mechanisms[98]. This review demonstrated that HDIPs with cysteine protease activity consistently and significantly reduced pro-inflammatory cytokine levels and increased anti-inflammatory cytokine levels, in line with the existing literature. Another mechanistic class that was widely assessed were the cathelicidin-like HDIPs. These are the so-called helminth defense molecules (HDMs) secreted by trematodes such as *Fasciola hepatica*, *Schistosoma mansoni* and *Schistosoma japonicum*, that share that share structural and functional similarities

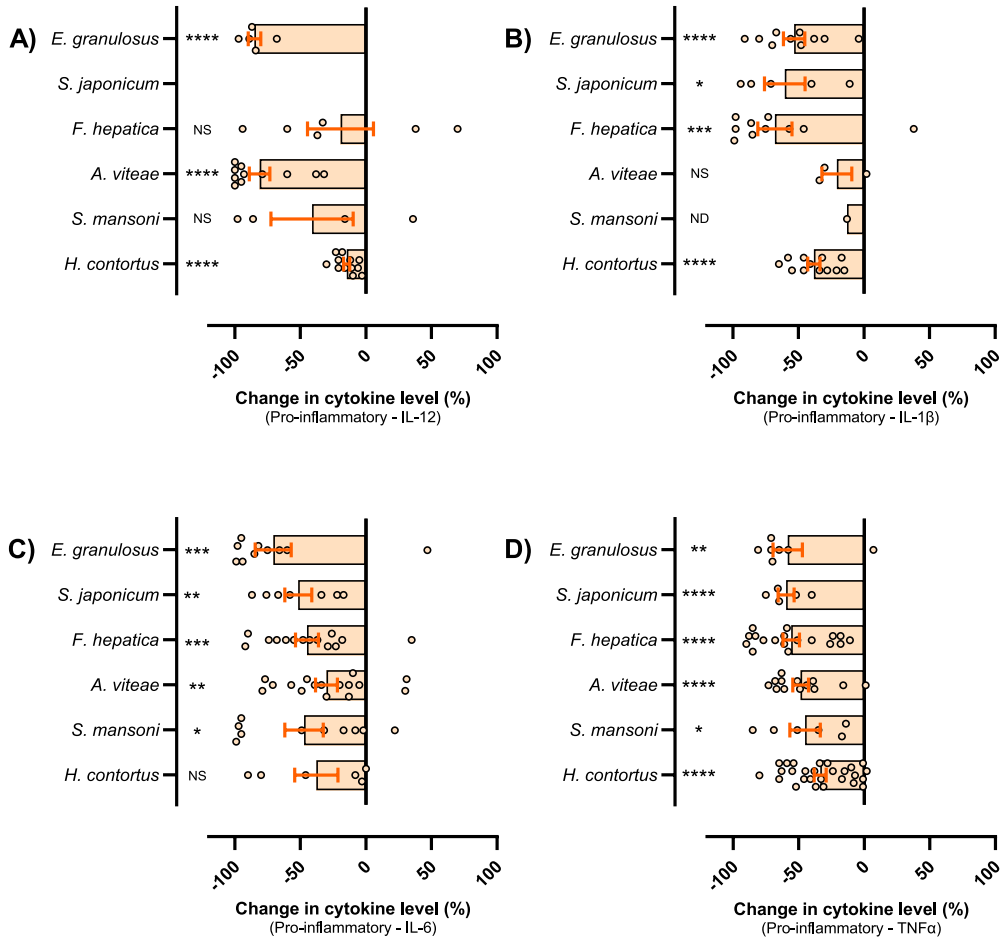


Fig. 6. Effect of HDIPs from specific species on pro-inflammatory cytokine levels. The effect of the HDIPs from the most widely used species on (**A**) IL-12, (**B**) IL-1β, (**C**) IL-6 and (**D**) TNFα cytokine levels. Each data point represents a specific record extracted from Table 1/Supplementary Excel file, and the mean ± sem is also shown. Data were analysed by one-sample test with the hypothesised population mean set to zero. $^{****}P<0.0001$, $^{***}P<0.001$, $^{**}P<0.01$ and $^{*}P<0.05$. NS, not-significantly different to zero; ND, not done as too few points.

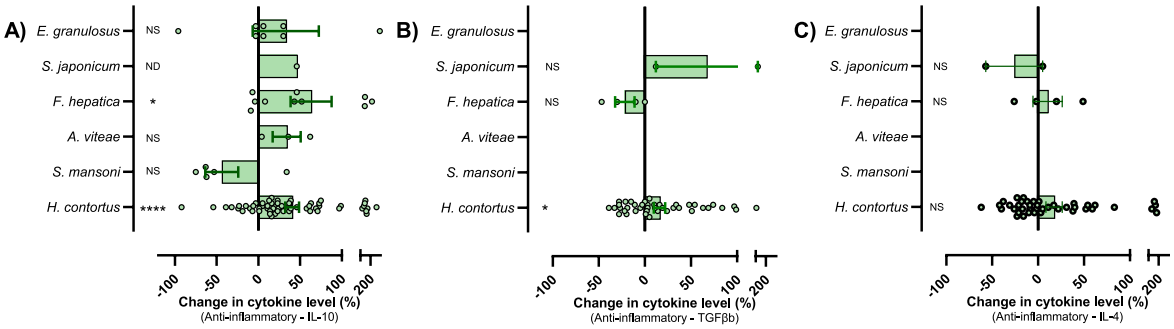


Fig. 7. Effect of HDIPs from specific species on anti-inflammatory cytokine levels. The effect of the HDIPs from the most widely used species on (**A**) IL-10, (**B**) TGFβ and (**C**) IL-4 cytokine levels. Each data point represents a specific record extracted from Table 1/Supplementary Excel file, and the mean ± sem is also shown. Data were analysed by one-sample test with the hypothesised population mean set to zero. $^{****}P<0.0001$ and $^{*}P<0.05$. NS, not-significantly different to zero; ND, not done as too few points.

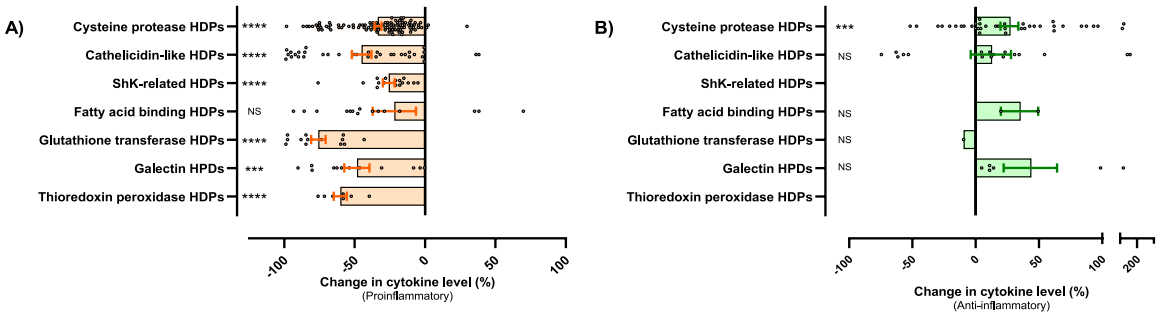


Fig. 8. Effect of mechanistic classes of HDIPs on cytokines. The effect of the HDIPs from different mechanistic classes was assessed on A) pro-inflammatory (IL-12, IL-1β, IL-6 and TNFα) and B) anti-inflammatory (IL-10, TGFβ and IL-4) cytokine levels. Each data point represents a specific record extracted from Table 1/ Supplementary Excel file, and the mean ± sem is also shown. Data were analysed by one-sample test with the hypothesised population mean was set to zero. ****$P < 0.0001$ and ***$P < 0.001$.

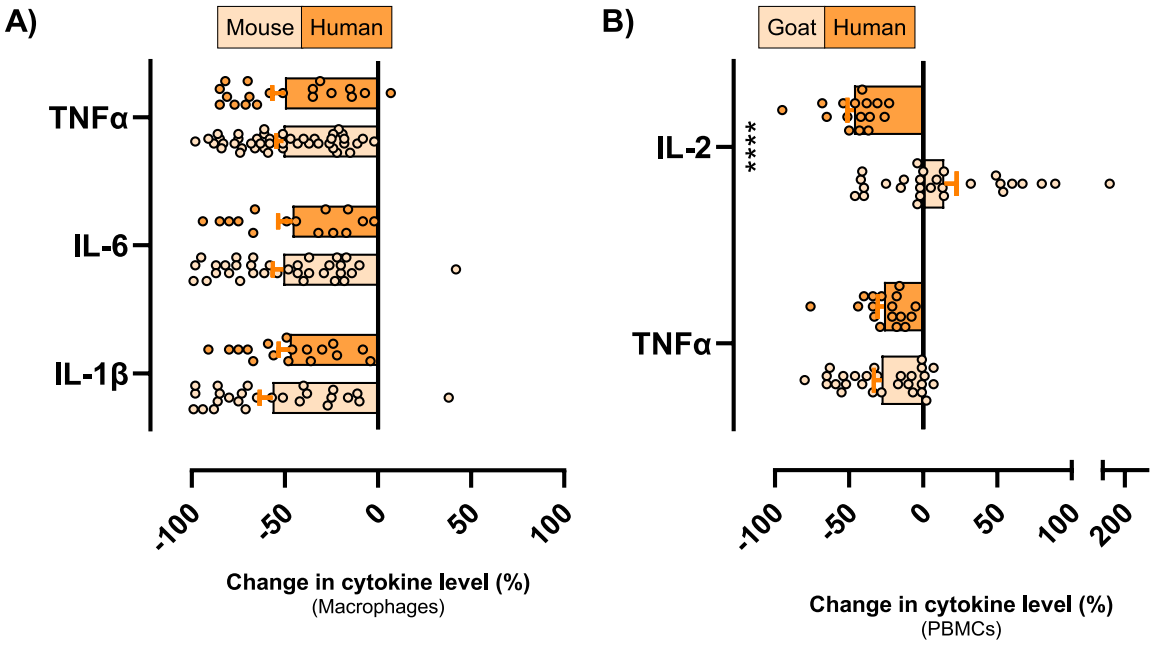


Fig. 9. Effect of cell species on change in cytokine levels by HDIPs. The effect of HDIPs on selected pro-inflammatory cytokine levels in (**A**) macrophages derived from mice and humans, and (**B**) PBMCs derived from goats and humans. Each data point represents a specific record extracted from Table 1/Supplementary Excel file, and the mean ± sem is also shown. Data were analyzed by two-way ANOVA with *post-hoc* Bonferroni. ****$P < 0.0001$ Goat vs. Human.

with mammalian cathelicidin[100,101]. Like the cysteine proteases, these have multiple mechanisms through which they can enable trematode infection and immune suppression of the host including molecular mimicry, LPS-binding and sequestration, and inhibition of the NLRP3 inflammasome activation[102]. In the present review, the cathelicidin-like HDIPs also profoundly reduced pro-inflammatory cytokine levels but effects on anti-inflammatory cytokines were not significant overall. Similarly, the other mechanistic classes assessed included ShK-related HDIPs, fatty acid binding HDIPs, glutathione transferase HDIPs, galectin HDIPs, and thioredoxin peroxidase HDIPs all of which, like the cathelicidin-like HDIPs, significantly reduced proinflammatory cytokine levels.

One unexpected aspect of the data consolidation in this review was the finding of a greater efficacy of HDIPs (greater suppression of pro-inflammatory cytokines) in macrophages compared with PBMCs. However, this is likely simply due to the heterogeneity of the PBMC population which includes many populations of lymphocytes (including T-cells, B-cells and natural killer cells) as well as monocytes which can be considered immature macrophages. Thus, relative to more uniform macrophage cultures, PBMC cultures are likely to have variable responsivity to the main inflammagens used and consequently, variability responsivity to the HDIPs. Additionally, the helminth molecules may also have a broad range of cellular targets—so some may interact

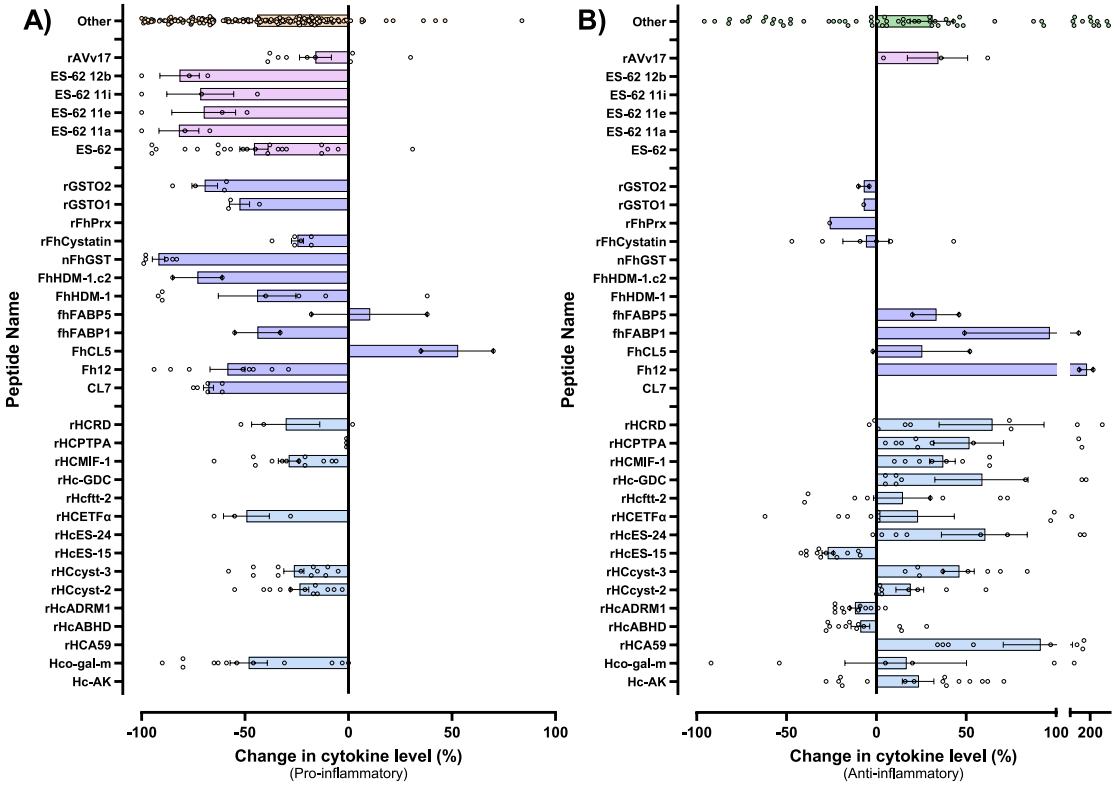


Fig. 10. Effect of specific HDIPs on cytokine levels. The effect of named HDIPs from *H. contortus* (blue), *F. hepatica* (purple) and *A. viteae* (pink) on (**A**) pro-inflammatory (IL-12, IL-1β, IL-6 and TNFα) and (**B**) anti-inflammatory (IL-10, TGFβ and IL-4) cytokine levels. Each data point represents a specific record extracted from Table 1/Supplementary Excel file, and the mean ± sem is also shown.

with, and modulate, the activity of all cells within PBMC cultures, whereas others may only have specificity for one cell type—this has not been explored for many of the proteins being examined here, but might also explain the difference in efficacy. The effect of cell species from which the PBMCs were derived was another unexpected finding with HDIPs reducing IL-2 in human PBMCs but not goat PBMCs. This highlights the importance of cell species as a consideration for study design. Another interesting aspect of the current systematic review is that it revealed the paucity of studies using other, critically important, immune cells. For example, there was only a single study each in which the immunomodulatory effect of HDIPs in mast cells[51] or microglia[34] was assessed. This highlights an important gap in literature as there is potential for the HDIPs to be effective immunomodulators in allergic and/or neuroinflammatory conditions. Another gap in the literature that was identified in this systematic review was the lack of variability in the inflammagen used with most studies using LPS. LPS is a gram-negative bacterial endotoxin that is recognized by Toll-like receptor 4 (TLR4) on multiple cell types, causing a signaling cascade which leads to the activation of NF-kB, triggering the release of proinflammatory molecules like TNFα, IL-6, and nitric oxide[103]. Although LPS-induced inflammation is a widely accepted and common model for many inflammatory conditions, there is a need to test whether HDIPs can mitigate the effects of other clinically relevant inflammatory triggers, not only other pathogen-associated molecular patterns, but also damage-associated molecular patterns.

While this review focused on assessing the efficacy of HDIPs (in modulating cytokine levels) in cellular models, several studies have also assessed their efficacy in animal models on inflammatory disease such as inflammatory bowel disease[4], multiple sclerosis[92], rheumatoid arthritis[104] and asthma[105]. The success of these, and other studies, studies led to a series of clinical trials of helminth therapy in which patients are infected with specific helminths to modulate the immune system and treat their inflammatory and autoimmune diseases. Infection with the hookworm, *Necator americanus*, for example, has been assessed in clinical trials of ulcerative colitis[106], multiple sclerosis[107] and celiac disease[108] with mixed results in terms of both efficacy and safety. This highlights the rationale for continued research and development of HDIPs as therapeutic drugs as these would reduce the risks associated with live parasitic infection. To date, only one clinical trial of a HDIP has been completed (NCT02281916) in which P28GST, a *Schistosoma haematobium*-derived glutathione S-transferase, was tested in patients with Crohn's disease with some evidence of efficacy[109].

One limitation of this review, as with all systematic reviews, is the potential for important studies to have been omitted due to the systematic nature of the search and screening. While systematic reviews minimise bias by using a rigorous and predefined method to find relevant research, there is a need to balance sensitivity (finding all relevant studies) and specificity (reducing irrelevant results). While high sensitivity uses broader search terms and reduces the risk of excluding relevant studies, it can also lead to more irrelevant results and a heavier

screening burden. In contrast, high specificity uses more specific search terms to identify highly relevant studies and reduce screening workload, but this risks excluding relevant studies. Despite these inherent limitations of systematic approaches to literature appraisal, this review systematically consolidates and summarises the effect of immunomodulatory HDIPs in cellular model of inflammation. It clearly demonstrates that suppression of pro-inflammatory, and enhancement of anti-inflammatory, cytokine expression and production in response to inflammagen stimulation in immune cells is a property of many HDIPs from many species. The review also revealed important gaps in this literature highlighting the opportunity to explore the immunomodulatory efficacy of HDIPs in other cell types using other inflammatory stimuli to determine their potential for other immune system disorders heretofore relatively unexplored. Consolidating this literature may direct future research into the use of HDIPs in a wider variety of preclinical models in order to determine their broader therapeutic potential.

Data availability

All data is available in the Supplementary Excel file.

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Declarations

Competing interests

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Additional information

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Correspondence and requests for materials should be addressed to E.D.

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