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Review article

An overview on *human* serum lectins

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ABSTRACT

An extensive literature survey done on the various naturally occurring lectins in human serum upon its salient features such as methods of detection, level and sites of synthesis, binding specificity, cation dependency, modes of isolation, molecular and functional characterization way back from 1930s to till date was presented in a tabulated section. In addition, the generation of lectin and other immune molecules in vertebrates upon treatment with exogenous elicitors has also been framed in a tabular form. Furthermore, *ANEW* lectin induced in human serum *for the very first time* by an exogenous elicitor was detected, isolated and characterized by us whose features are also tabulated explicitly.

1. Introduction

1.1. Definition

Lectins or agglutinins are proteins/glycoproteins of non-immune origin with a unique ability to specifically and reversibly bind to carbohydrate structures present on cell surfaces, extracellular matrices or secreted glycoproteins (Goldstein et al., 1980; Barondes, 1988; Weis, 1997; Sharon, 2007). Each lectin molecule may possess mono-, di-, or multi-valent carbohydrate binding sites, whereas the lectin with agglutinating property, called agglutinin, necessarily contains more than two such sites per molecule.

1.2. Important discoveries

Lectin molecules was first discovered by Stillmark in 1888 (as cited in Goldstein and Hayes, 1978) in the castor-bean (*Ricinus communis*) extracts, which was named as ricin. Subsequently, Camus (1899) first reported the presence of agglutinins in the albumen gland from garden snail, *Helix pomatia*. Noguchi (1903) described the presence of natural agglutinins in sera of lobster (*Homarus americanus*) and horse-shoe crab (*Limulus polyphemus*) and these findings represent the first report on the occurrence of lectins in animals.

1.3. Distribution

Lectin molecules are seen in a wide range of living organisms such as microbes (Sasmal et al., 1992), plants (Goldstein and Hayes, 1978), animals and humans (Olden and Parent, 1987; Mullainadhan and Renwrantz, 1989; Turner, 1996; Kilpatrick, 2002). In humans, the lectin molecules were first detected in blood plasma/serum, and over 20 distinct types of lectins including selectins and galactins were subsequently reported to occur in a variety of cells, tissues, or organs (Baenziger and Maynard, 1980; Ikeda et al., 1987; Stamenkovic and Seed, 1990; Zanetta et al., 1992; Kanses, 1996; Yaron et al., 1997; Kilpatrick, 2000).

1.4. Classification of human serum lectins

Six distinct naturally occurring lectins have been detected in the serum or plasma obtained from human blood, namely, C-reactive protein (Tillett and Francis, 1930) serum amyloid protein (Cathcart et al., 1967), H-ficolin (Inaba and Okochi, 1978), mannan-binding lectin (Kawasaki et al., 1983), tetranectin (Clemmensen et al., 1986) and L-ficolin (Matsushita et al., 1996). On the basis of its structural and biochemical characteristics, the six humoral lectins have been classified into four families, namely, pentraxins (C-reactive protein and serum amyloid protein), collectin (mannan-binding lectin), ficolins (H-ficolin and L-ficolin) and tetranectin.

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Table 1. A summary of literature pertaining to methods employed to detect various lectins naturally occurring in human blood (plasma/serum).

S. No.	Name of Lectin (Family)	Methods of Detection	References
1.	C - reactive protein	Precipitation	
	(Pentraxin)	• Visual	Tillett and Francis (1930)
		• Radial immunodiffusion	Kushner and Somerville (1970)
		• Capillary precipitin test	
		• Immunoelectrophoresis	
		• Double immunodiffusion	Kaplan and Volanakis (1974)
		• Nephelometry	Di Camelli et al. (1980)
		• Crossed immunoelectrophoresis	de Beer et al. (1982)
		• Spot immunoprecipitate assay	Wadsworth et al. (1985)
		Agglutination	
		• Heat - killed pneumococci	Tillett and Francis (1930)
		• Pneumococcal capsular polysaccharide - coated sheep RBC	Gal and Miltényi (1955)
		• Lipid emulsion	Rowe et al. (1986)
		• Very low density lipoproteins	
		• Antibody-coated latex particles	Das et al. (2004)
		Pneumococcal capsular swelling reaction	Hedlund (1947)
		Radioimmunoassay	Shine et al. (1981)
		Immunoradiometric assay	Shapiro and Shenkin (1989)
		Enzyme-linked immunosorbent assay	Nunomura et al. (1990)
2.	Serum amyloid protein	Precipitation	
	(Pentraxin)	• Double immunodiffusion	Cathcart et al. (1967)
		• Immunoelectrophoresis	
		• Double immunodiffusion	Pepys et al. (1977)
		• Immunoelectrophoresis	
		• Crossed immunoelectrophoresis	
		• Rocket immunoelectrophoresis	Sørensen et al. (1995)
		Agglutination	
		• Complement - coated sheep RBC	Hutchcraft et al. (1981)
		• Rat & horse RBC	Hamazaki (1988)
3.	H – Ficolin	Precipitation	
	(Ficolin)	• Double immunodiffusion	Inaba and Okochi (1978)
		• Double immunodiffusion	Yae et al. (1991)
		• Immunoelectrophoresis	
		• Enzyme immunoassay (ELISA)	
		Agglutination	
		•Bacterial lipopolysaccharide-coated human RBC	Sugimoto et al. (1998)
		Time resolved fluorimetry	Krarup et al. (2004)
4.	Mannan - binding lectin	Radiolabelled ligand binding assay	Kawasaki et al. (1983)
	(Collectin)		
		Enzyme - linked immunosorbent assay	Summerfield and Taylor (1986)
		Enzyme - linked lectin immunosorbent assay	Thiel et al. (1992)
5.	Tetranectin	Precipitation	Clemmensen et al. (1986)
		• Rocket immunoelectrophoresis	
		• Crossed immunoelectrophoresis	
		Enzyme immunoassay (ELISA)	Thougaard et al. (2001)
6.	L – Ficolin	*N* - acetylglucosamine elution from affinity matrix	Matsushita et al. (1996)
	(Ficolin)		
		Enzyme - linked immunosorbent assay	Le et al. (1998)
		Time resolved fluorimetry	Krarup et al. (2004)

1.5. Binding specificity

Lectins primarily recognize and bind to specific carbohydrate structures present on the surface of target cells and molecules (Sharon, 2007). They exhibit great diversity in sugar binding specificity. Thus, the lectins are known to specifically recognize the whole sugar, a specific part of a sugar, a sequence of sugars, or their glycosidic linkages (Ravindranath et al., 1985; Murali et al., 1999). Besides, a few studies have demonstrated that the lectins especially from diverse animal sources can additionally recognize certain non-carbohydrate ligands including peptide motif and even simple chemicals containing appropriate determinant structures (Gabius, 1994; Kawagishi et al., 1994; Gokudan et al., 1999; Maheswari et al., 2002). Such lectins are likely to accomplish their reactivity through a common binding site (Maheswari et al., 2002) or two separate structural domains (Gabius, 1994).

Table 2. A profile of levels and site of synthesis of various lectins naturally occurring in human plasma/serum.

S. No.	Name of Lectin	Concentration (μg/ml)	References	Site of Synthesis	References
1.	C - reactive protein	0.5–2	Pepys and Baltz (1983)	Liver	Hurlimann et al. (1965)
			Das et al. (2004)		
2.	Serum amyloid protein	20–40	Pepys and Baltz (1983)	Liver	Pepys and Baltz (1983)
3.	H – Ficolin	7–23	Yae et al. (1991)	Liver & lungs	Akaiwa et al. (1999)
4.	Mannan - binding lectin	0.01–6.40	Terai et al. (1993)	Liver	Summerfield and Taylor (1986)
			Kilpatrick (1997)		Kurata et al. (1994)
5.	Tetranectin	8–17	Thougaard et al. (2001)	Lungs, spleen, heart,	Berglund and Petersen (1992)
				skeletal muscle, liver &	
				brain	
6.	L – Ficolin	1.1–12.8	Kilpatrick et al. (1987)	Liver	Matsushita et al. (1996)

1.6. Structure of humoral lectins in human serum

Molecular nature of all the six naturally occurring lectins isolated from human plasma/serum have been studied by estimating the native molecular weight using various methods including analytical ultracentrifugation, gel filtration, sucrose gradient centrifugation and polyacrylamide gradient gel electrophoresis. Accordingly, the native molecular weight estimates for various lectins are: 118–140 kDa for C-reactive protein (Gotschlich and Edelman, 1965; Siegel et al., 1974), 240–300 kDa for serum amyloid protein (Hamazaki, 1986; Binette et al., 1974), 520–688 kDa for H-ficolin (Yae et al., 1991), 200–700 kDa for mannan-binding lectin (Taylor and Summerfield, 1987; Thiel et al., 1992), 68 or 90 kDa for tetranectin (Clemmensen et al., 1986; Thougaard et al., 2001) and 320 or 650 kDa for L-ficolin (Matsushita et al., 1996; Krarup et al., 2004). The analysis of subunit characteristics mostly by SDS-PAGE under reducing conditions revealed that various isolated lectin molecules are composed of identical subunits, but the number of subunits in different lectins varied between 3 and 22 (Thougaard et al., 2001; Super et al., 1989) and each subunit with molecular mass ranging from 20 to 40 kDa (Gotschlich and Edelman, 1965; Le et al., 1997).

1.7. Salient functional features

The actual physiological and immunological functions of many lectins remain to be precisely determined. However, in invertebrates physiological functions have been demonstrated for lectins such as feeding, larval settlement, embryonic development and metamorphosis. Further, their participation in various immuno-defense processes, namely, wound repair, clearance and opsono-phagocytosis of foreign targets are also well established (Coombe et al., 1984; Mullainadhan and Renwrantz, 1986; Olafsen, 1988; Smith and Chisholm, 1991; Cooper et al., 1992; Beck et al., 1994; Arason, 1996). Lectins in mammalian systems have also been suggested to play diverse roles in physiology, development and pathological states (Varki, 1993). In humans, the lectins detected within various cells, tissues or organs have been reported to mediate diverse physiological functions such as removal of aged cells or modified plasma glycoproteins, cell adhesion and signal transduction. Furthermore, they are involved in various immunological processes, namely, receptors for pathogens, opsono-phagocytosis and developmental regulation of different immune cells (Baenziger and Maynard, 1980; Lennartz et al., 1987; Catalina et al., 1999; Ackerman et al., 1993; Wang et al., 1998). Humoral lectins detected in human blood has been mainly focussed towards elucidation of their role in immune processes, because they are considered as key players of innate immunity and emerging as important components in the molecular mechanisms of inflammation and initiation of internal host defence responses (Wang et al., 1998; Catalina et al., 1999; Sharon and Lis, 2004).

1.8. Survey of literature on humoral lectins in human plasma/serum

Six distinct naturally occurring lectins have been detected in the serum or plasma obtained from human blood. As presented in Table 1, these humoral lectins include C-reactive protein, serum amyloid protein, H-ficolin, mannan-binding lectin, tetranectin, and L-ficolin. Among these molecules, C-reactive protein was first discovered in 1930 by Tillet & Francis, which is commonly known as an acute phase protein. However, this protein was later found to bind additionally specific carbohydrates (Gotschlich and Liu, 1967; Soelter and Uhlenbruck, 1986), and it is also, therefore, considered as a lectin (Kilpatrick, 2002). The chronological discovery of other five humoral lectins is as follows: serum amyloid protein (Cathcart et al., 1967), H-ficolin (Inaba and Okochi, 1978), mannan-binding lectin (Kawasaki et al., 1983), tetranectin (Clemmensen et al., 1986), and L-ficolin (Matsushita et al., 1996). Based on the structural and biochemical characteristics, the six humoral lectins have been classified into four families, namely, pentraxins (C-reactive protein and serum amyloid protein), collectin (mannan-binding lectin), ficolins (H- and L-ficolins) and tetranectin (Table 1).

1.9. Methods employed for detection of humoral lectins

As presented in Table 1, various methods were employed to detect the presence of lectins in human serum or plasma. These include mainly precipitation, agglutination, antibody-based immunoassays and fluorimetry. Hemagglutination assay is relatively a simpler method for detection of lectins or agglutinins (Sharon and Lis, 1989). But it appears that none of the humoral lectins were detectable by this assay using native vertebrate RBC. However, C-reactive protein, serum amyloid protein and H-ficolin have been detected by their ability to agglutinate, respectively, pneumococcal capsular polysaccharide-coated sheep RBC (Gal and Miltényi, 1955), complement-coated sheep RBC (Hutchcraft et al., 1981) and bacterial lipopolysaccharide-coated human RBC (Sugimoto et al., 1998). Exceptionally, Hamazaki (1988) has reported the ability of serum amyloid protein isolated from human serum to cause agglutination of horse and rat RBC.

1.10. Levels and site of synthesis of humoral lectins

The levels and site of synthesis of various lectins naturally occurring in plasma or serum of normal human blood have been presented in Table 2. Among various lectins, serum amyloid protein is most abundantly present in systemic blood circulation (20–40 μg/ml), whereas mannan-binding lectin appears to occur at the lowest concentration (0.01–6.40 μg/ml). Liver has been invariably identified as the site of synthesis for all the humoral lectins so far described. However, additional sites such as lungs for H-ficolin, and lungs as well as other multiple tissues and organs for tetranectin have been documented.

Table 3. Binding specificity and divalent cation dependency of various lectins detected in human blood (plasma/serum) and other sources.

S. No.	Binding Specificity		Divalent Cation Dependency		References
	Ligands recognized	Best Ligand (s)	Cations tested	Dependency	
1. C-reactive protein (Source: serum/plasma, pleural, peritoneal or ascitic fluids)					
	Precipitation assay				
1.	Pneumococcal CPS	Pneumococcal CPS	Not tested	Not relevant	Tillett and Francis (1930)
2.	Pneumococcal CPS	Pneumococcal CPS	Ca^{2+}	Ca^{2+}	Abernathy and Avery (1941)
3.	Pneumococcal CPS, polymer of	Pneumococcal CPS, polymer of	Not tested	Not relevant	Gotschlich and Liu (1967)
	N - acetylgalactosamine - phosphate	*N* - acetylgalactosamine – phosphate			
4.	Poly - L - lysine, poly - L - arginine,	Protamine sulphate	Ca^{2+}	Not dependent	Di Camelli et al. (1980)
	protamine sulphate, poly - L - ornithine				
5.	Galactan	Galactan	Ca^{2+}	Ca^{2+}	Soelter and Uhlenbruck (1986)
	Inhibition of CRP - CPS precipitation assay				
6.	Phosphate monoesters:				
	α - Glycerophosphate	5′- Uridine monophosphate	Ca^{2+}	Ca^{2+}	Gotschlich and Edelman (1967)
	5′- Adenine monophosphate				
	5′- Uridine monophosphate				
	5′- Cytidine monophosphate				
7.	Phosphorylcholine	Phosphorylcholine	Not tested	Not relevant	Kaplan and Volanakis (1974)
	L - α - Glycerophosphorylcholine				
	DL - α - Glycerophosphate				
	5' - Cytidine monophosphate				
	Inhibition of CRP - CPS/poly - L - lysine precipitation assay				
8.	Polybrene, phosphorylcholine,	Polybrene	Not tested	Not relevant	Siegel et al. (1975)
	tetra - L – lysine				
	Inhibiton of CRP - CPS mediated complement fixation				
9.	Glucosamine - 6 - phosphate	*N* - acetylgalactosamine – phosphate	Not tested	Not relevant	Gotschlich and Liu (1967)
	Mannose - 6 - phosphate				
	Galactosamine - 6 - phosphate				
	N - acetylglucosamine - phosphate				
	N - acetylgalactosamine - phosphate				
10.	Phosphorylcholine	Phosphorylcholine	Not tested	Not relevant	Kaplan and Volanakis (1974)
	DL - α - Glycerophosphate				
	5′- Cytidine monophosphate				
	Inhibition of CRP - lecithin/sphingomyelin mediated complement fixation				
11.	Phosphorylcholine	Phosphorylcholine	Not tested	Not relevant	Kaplan and Volanakis (1974)
	L - α - Glycerophosphorylcholine				
	DL - α - Glycerophosphate				
	5' - Cytidine monophosphate				
	Complement activation				

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Table 3 (*continued*)

S. No.	Binding Specificity		Divalent Cation Dependency		References
	Ligands recognized	Best Ligand (s)	Cations tested	Dependency	
12.	Protamine sulphate	Protamine sulphate	Ca^{2+}	Ca^{2+}	Siegel et al. (1974)
13.	Protamine, poly - L - lysine,	Protamine, poly - L - lysine,	Not tested	Not relevant	Siegel et al. (1975)
	histone, myelin basic protein,	histone, myelin basic protein			
	leukocyte cationic protein,				
	poly - L – arginine				
	Solid - phase ligand binding assay				
14.	Low density lipoprotein	Low density lipoprotein	Ca^{2+}	Ca^{2+}	de Beer et al. (1982)
	Very low density lipoprotein				
	Enzyme - linked immunosorbent assay				
15.	Fibronectin	Fibronectin	Ca^{2+}	Ca^{2+}	Salonen et al. (1984)
16.	Phosphorylcholine	β - D - Gal - (1–3) - D - GalNAc			
	A variety of di- and tri- saccharides	β - D - Gal - (1–4) β - D - Gal -	Not tested	Not relevant	Köttgen et al. (1992)
	with terminal galactose:	(1–4) - D - GlcNAc			
	α - D - Gal - (1–4) - D - Gal				
	β - D - Gal - (1–6) - D - Gal				
	β - D - Gal - β - D - Thio - Gal				
	β - D - Gal - (1–3) - D - GalNAc				
	β - D - Gal - (1–6) - D - GalNAc				
	β - D - Gal - (1–4) - D - GlcNAc				
	β - D - Gal - (1–6) - D - GlcNAc				
	β - D - GlcNAc - (1–6) - D - GlcNAc				
	β - D - Gal - (1–4) β - D - Gal - (1–4) - D - GlcNAc				
17.	Phosphorylcholine	Phosphorylcholine	Ca^{2+}	Ca^{2+}	Culley et al. (2000)
	Galactose - 6 - phosphate	Galactose - 6 - phosphate			
	Galactose -1 - phosphate				
	Glucose - 6 - phosphate				
	Glucose - 1 - phosphate				
	Mannose - 6 - phosphate				
	Mannose -1 - phosphate				
	Fructose - 6 - phosphate				
	Fructose - 1 - phosphate				
18.	Protein A from *Streptococcus aureus*	Protein A	Ca^{2+}	Not dependent	Das et al. (2004)
	Radiolabelled fluid phase binding assay				
19.	Lipophosphoglycan	Lipophosphoglycan	Ca^{2+}	Ca^{2+}	Culley et al. (1996)
	Radiolabelled lectin binding assay				
20.	Native and modified low density	Phosphorylcholine	Ca^{2+}	Ca^{2+}	Taskinen et al. (2002)
	lipoprotein, cholesterol,	Cholesterol			
	Phosphorylcholine				
2. Serum amyloid protein (Source: plasma/serum or ascitic fluid)					
	Solid phase direct binding assay				
1.	Agarose, agar, sulphated polyacrylamide	Agarose	Ca^{2+}	Ca^{2+}	Pepys et al. (1977)
2.	Heparin, agarose	Heparin	Ca^{2+}	Ca^{2+}	Thompson and Enfield (1978)
3.	Cyclic and non - cyclic 4, 6 pyruvate	Cyclic 4, 6 pyruvate acetal of	Ca^{2+}	Ca^{2+}	Hind et al. (1984)
	acetal of galactose	Galactose			

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Table 3 (*continued*)

S. No.	Binding Specificity		Divalent Cation Dependency		References
	Ligands recognized	Best Ligand (s)	Cations tested	Dependency	
	Solid phase ligand binding assay				
4.	Fibronectin, C4 - binding protein	Not reported	Ca^{2+}	Ca^{2+}	de Beer et al. (1981)
5.	DNA, chromatin	DNA	Ca^{2+}	Ca^{2+}	Pepys and Butler (1987)
6.	C4 - binding protein	C4 - binding protein	Ca^{2+}	Ca^{2+}	Frutos et al. (1995)
7.	Laminin	Laminin	Ca^{2+}, Mg^{2+}, Mn^{2+}, Zn^{2+}	Ca^{2+}	Zahedi (1997)
	Agglutination of complement - coated sheep RBC				
8.	Complement component - C3b	C3b	Ca^{2+}	Ca^{2+}	Hutchcraft et al. (1981)
	Radiolabelled fluid phase binding assay				
9.	Zymosan	Zymosan	Ca^{2+}, Cu^{2+}, Mg^{2+}, Mn^{2+}, Ni^{2+}, Zn^{2+},Cd^{2+}, Ba^{2+}, Co^{2+}	Ca^{2+}, Cu^{2+}, Cd^{2+}, Zn^{2+}	Potempa et al. (1985)
	Inhibition of radiolabelled lectin binding assay				
10.	Galactose	Galactose	Ca^{2+}, Mg^{2+}	Ca^{2+}	Hamazaki (1986)
	Inhibition of rabbit RBC agglutination				
11.	Simple substances:				
	Non - acetylated and *N* – acetylated 2 - O - α - D-glucopyranosyl- O - β - D - galactopyranosyl hydroxylysine Stachyose	*N* - acetylated - 2 - O - α - D – glucopyranosyl - O - β - D -galactopyranosylhydroxylysine	Not tested	Not relevant	
	Glycoconjugates:				
	Orosomucoid, desialylated orosomucoid, human glycophorin	Desialylated bovine erythrocyte glycoprotein	Not tested	Not relevant	
	Desialylated glycophorin				
	Bovine erythrocyte glycoprotein				
	Desialylated bovine erythrocyte				
	Glycoprotein				
	Radiolabelled ligand binding and inhibition assays				
12.	Glycosaminoglycans:				
	Heparan, dermatan sulphate,	Heparin	Ca^{2+}, Ba^{2+}, Cd^{2+}, Cu^{2+},	Ca^{2+}, Cd^{2+}	Hamazaki (1987)
	Heparin, chondroitin - 4 - sulphate,		Mg^{2+}, Mn^{2+}, Sr^{2+}, Zn^{2+}		
	Chondroitin - 6 - sulphate				
	Hyaluronic acid				
	Inhibition of radiolabelled lectin binding assay				Hamazaki (1988)
13.	Glycosaminoglycans:				
	Chondroitin - 4 - sulphate	Hyaluronic acid	Not tested	Not relevant	
	Dermatan sulphate				
	Chondroitin - 6 - sulphate				
	Heparan sulphate				
	Hyaluronic acid				
	Keratan sulphate				
	Chondroitin				
	Inhibition of rabbit RBC agglutination				
14.	Dermatan sulphate	Hyaluronic acid	Not tested	Not relevant	
	Heparan sulphate				
	Hyaluronic acid				

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Table 3 (*continued*)

S. No.	Binding Specificity		Divalent Cation Dependency		References
	Ligands recognized	Best Ligand (s)	Cations tested	Dependency	
	Enzyme - linked fluorescent immunoassay				
15.	Zymosan, ovalbumin, porcine thyroglobulin	Zymosan	Ca^{2+}	Ca^{2+}	Kubak et al. (1988)
	C3bi, β - glucuronidase				
	Inhibition of SAP polymerisation				
16.	Heparin, heparan sulphate,	Dextran sulphate	Not tested	Not relevant	Hamazaki (1989)
	Dermatan sulphate	(MW 10^6 Da)			
	Chondroitin - 6 - sulphate				
	Chondroitin - 4 - sulphate				
	Dextran sulphate				
	Enzyme - linked immunosorbent assay				
17.	Heparin, heparan sulphate,	Heparin	Ca^{2+}	Ca^{2+}	Danielsen et al. (1997)
	Dermatan sulphate				
	Chondroitin - 6 - sulphate				
3. H-Ficolin (Source: serum/plasma)					
1.	**Solid phase direct binding assay**				Sugimoto et al. (1998)
	N - acetylgalactosamine	*N* - acetylgalactosamine	Not tested	Not relevant	
	N - acetylglucosamine	*N* - acetylglucosamine			
2.	**Agglutination of LPS - sensitized human O RBC**				
	LPS from *Salmonella typhimurium*	LPS from *Salmonella typhimurium*	Ca^{2+}	Not dependent	
	Salmonella minnesota,				
	Escherichia coli				
3.	**Inhibition of LPS-sensitized human O RBC agglutination**				
	N - acetylgalactosamine				
	N - acetylglucosamine				
	D – fucose	D - fucose	Not tested	Not relevant	
4. Mannan - binding lectin (Source: serum/plasma)					
	Inhibition of radiolabelled ligand binding assay				
1.	*N* - acetylmannosamine	*N* - acetylmannosamine	Ca^{2+}	Ca^{2+}	Kawasaki et al. (1983)
	N - acetylglucosamine				
	Mannose, L - fucose, glucosamine,				
	Mannosamine				
	Electroblot analysis				
2.	D - glucose, D - galactose,	Invertase, mannan	Ca^{2+}	Ca^{2+}	Summerfield and Taylor (1986)
	L - fucose, *N* - acetylglucosamine,	B - galactosidase,			
	α - methyl - D - mannoside	ovalbumin, L - fucose,			
	Invertase, mannan, β - galactosidase,	α - methyl - D - mannoside			
	ovalbumin, orosomucoid	*N* - acetylglucosamine			
	Enzyme - linked immunosorbent assay				Taylor and Summerfield (1987)
3.	MBP1: *N* - acetylglucosamine	*N* - acetylglucosamine	Ca^{2+}	Ca^{2+}	
	N - acetylmannosamine, mannose,	*N* - acetylmannosamine			
	fucose, glucose, mannan,	mannose, fucose			
	invertase, orosomucoid				
	MBP2: mannose, fucose, mannan, invertase, orosomucoid, asialoorosomucoid	Mannose, mannan,	Ca^{2+}	Ca^{2+}	
		invertase, asialoorosomucoid			

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Table 3 (*continued*)

S. No.	Binding Specificity		Divalent Cation Dependency		References
	Ligands recognized	Best Ligand (s)	Cations tested	Dependency	
4.	Phospholipids:	Phosphatidylinositol	Not tested	Not relevant	Kilpatrick (1998)
	Phosphatidylserine				
	Phosphatidylinositol				
	Phosphatidylcholine				
	Complement activation				
5.	Zymosan	Zymosan	Ca^{2+}	Ca^{2+}	Lu et al. (1990)
	Enzyme - linked lectin immunosorbent assay				
6.	Mannose, *N* - acetylglucosamine	Mannose	Ca^{2+}	Ca^{2+}	Thiel et al.,1992
	galactose, glucose	*N* - acetylglucosamine			
	Enzyme - linked lectin binding assay				
7.	Mannose, glucose, L-fucose,	*N* - acetylglucosamine	Ca^{2+}	Ca^{2+}	Haurum et al. (1993)
	maltose, *N* -acetylmannosamine,				
	N-acetylglucosamine				
	Inhibition of phospholipid binding assay				
8.	Mannose, fucose, glucose, m - inositol,	*N* - acetylglucosamine	Not tested	Not relevant	Kilpatrick (1998)
	galactose, *N* -acetylglucosamine	m - inositol,			
5. Tetranectin (Source: serum/plasma)					
	Solid phase ligand binding assay				
1.	Plasminogen	Not reported	Ca^{2+}	Ca^{2+}	Clemmensen et al. (1986)
	Heparin		Ca^{2+}	Not dependent	
	Crossed immunoelectrophoresis				
2.	Chondroitin sulphate A, B & C	Not reported	Not tested	Not relevant	Clemmensen (1989)
	Heparan sulphate				
	Fucoidan				
3.	Lipoprotein (a)	Lipoprotein (a)	Not tested	Not relevant	Kluft et al. (1989a)
	Clot lysate analysis				
4.	Fibrin	Fibrin	Ca^{2+}	Ca^{2+}	Kluft et al. (1989b)
	Ligand blot analysis				
5.	Plasminogen	Plasminogen	Not tested	Not relevant	Westergaard et al. (2003)
	Hepatocyte growth factor				
	Tissue type plasminogen				
	Urokinase type plasminogen				
	Prothrombin				
6. L - Ficolin (Source: serum/plasma)					
	Dot - blot with radiolabelled lectin/solid phase direct binding assay				
1.	*N* - acetylglucosamine	Not reported	Ca^{2+}	Ca^{2+}	Matsushita et al. (1996)
	Asialofetuin				
	Elution from affinity gel matrix				
2.	*N* - acetylglucosamine	*N* - acetylglucosamine	Ca^{2+}	Not dependent	Le et al. (1997)
3.	*N* - acetylglucosamine	Not reported	Not tested	Not relevant	Le et al. (1998)
	N - acetylgalactosamine				
	Glutathione				

(*continued on next page*)

Table 3 (*continued*)

S. No.	Binding Specificity		Divalent Cation Dependency		References
	Ligands recognized	Best Ligand (s)	Cations tested	Dependency	
	Solid phase binding assay				
4.	Lipoteichoic acid	Lipoteichoic acid	Not tested	Not relevant	Lynch et al. (2004)
5.	*N* - acetylglucosamine	*N* - acetylglucosamine	Ca^{2+}	Not dependent	Krarup et al. (2004)
	N - acetylmannosamine	*N* - acetylmannosamine			
	N - acetylgalactosamine				
	N - acetylcysteine				
	N – acetylglycine				
	Acetylcholine				
6.	1, 3 - β - D - glucan	1, 3 - β - D - glucan	Not tested	Not relevant	Ma et al. (2004)

Abbreviations used: CPS = Capsular polysaccharide; CRP = C - reactive protein; LPS = Bacterial lipopolysaccharide; MBP = Mannan - binding protein; SAP = Serum amyloid protein.

1.11. Ligand-binding specificity

The ability of humoral lectins to recognize and bind specifically to various ligands has been examined using a variety of assays (Table 3). These include mainly the inhibition of lectin-mediated precipitation or agglutination reactions, complement fixation, solid phase binding assays, radiolabelled lectin binding assays, and antibody-based immunoassays such as ELISA and crossed-immunoelectrophoresis. Accordingly, phosphoryl choline, heparin, *N*-acetylgalactosamine, mannan, plasminogen and *N*-acetylglucosamine can be considered to be the best ligands, respectively, for C-reactive protein, serum amyloid protein, H-ficolin, mannan-binding lectin, tetranectin and L-ficolin (Kaplan and Volanakis, 1974; Thompson and Enfield, 1978; Summerfield and Taylor, 1986; Danielsen et al., 1997; Le et al., 1997; Sugimoto et al., 1998; Westergaard et al., 2003).

1.12. Divalent cation dependency

Most lectins, in general, require divalent cations which apparently stabilize the tertiary conformation of lectin polymers as well as help to structure their reactive sites (Marchalonis and Edelman, 1968; Reeke et al., 1974). As presented in Table 3, all six humoral lectins were analysed for divalent cation dependency by using various assay conditions. But these studies were restricted only with calcium ions and the only exception being serum amyloid protein tested with different divalent cations (Potempa et al., 1985; Hamazaki, 1987; Zahedi, 1997). However, it is notable that all the humoral lectins, with an exception of H-ficolin (Sugimoto et al., 1998), require Ca^{2+} to bind various appropriate ligands. In the case of serum amyloid protein, Cu^{2+}, Cd^{2+}, or Zn^{2+} could substitute for Ca^{2+}. However, a few conflicting reports indicate the divalent cation independent activity of C-reactive protein (Di Camelli et al., 1980; Das et al., 2004), tetranectin (Clemmensen et al., 1986) and L-ficolin (Le et al., 1997; Krarup et al., 2004). Indeed, all these humoral lectins naturally occurring in human blood have been isolated and purified to the desired level and then extensively studied for their physico-chemical and functional properties.

1.13. Methods adopted for isolation of humoral lectins

A perusal of literature presented in Table 4 reveals that several investigators have successfully attempted to isolate and purify each of the six lectins from human plasma or serum by employing various methods of their choice. Such chromatographic techniques include gel filtration, ion-exchange, hydrophobic interaction chromatography, and most frequently various types of affinity chromatography such as ligand-coupled, metal-affinity, immuno-affinity and lectin-affinity chromatography. It is notable from such studies presented in Table 4, that sequential multi-step procedures were employed for the isolation of these humoral lectins with the desired degree of purity. In general, affinity chromatography with versatile protocols has emerged as an ideal method for isolation of diverse kinds of biomolecules in native form and high degree of recovery from the starting crude samples (Heftmann, 2001). The humoral lectins in human plasma or serum adsorbed to the affinity gel matrix were recovered using various kinds of eluants (Table 4). These include simple carbohydrates as free ligands, divalent cation chelators (EDTA or sodium citrate), buffers at low or high pH and ionic strength.

1.14. Molecular nature of the isolated lectins

Molecular nature of all the six naturally occurring lectins isolated from human plasma/serum or pleural and peritoneal fluid as in the case of C-reactive protein (Table 5). They have estimated the native molecular weight of the lectins using various methods including analytical ultracentrifugation, gel filtration, sucrose gradient centrifugation and polyacrylamide gradient gel electrophoresis. On the other hand, the subunit characteristics of the isolated lectin molecules were examined frequently

Table 4. A summary of literature pertaining to methods adopted for isolation of various lectins from human blood (plasma/serum).

S. No.	Methods of isolation	Matrix used*	Eluants used in adsorption chromatography	References
1. C-reactive protein				
1.	Precipitation with ammonium sulphate (x2)	Not relevant	Not relevant	MacLeod and Avery (1941)
	↓			
	Precipitation by dialysis against water	Not relevant	Not relevant	
	Precipitation with sodium sulphate (x2)	Not relevant	Not relevant	
	↓			
	Precipitation by dialysis against water	Not relevant	Not relevant	
2.	Precipitation with barium sulphate	Not relevant	Not relevant	Ganrot and Kindmark (1969)
	↓			
	Precipitation with ammonium sulphate	Not relevant	Not relevant	
	↓			
	Gel adsorption	Reinagar	10 mM EDTA	
3.	GF	Sephadex G - 200	Not relevant	Kushner and Somerville (1970)
4.	Density gradient centrifugation	Not relevant	Not relevant	
5.	Precipitation with sodium sulphate	Not relevant	Not relevant	Siegel et al. (1974)
	↓			
	GF	Sephadex G - 200	Not relevant	
6.	Precipitation with ammonium sulphate (x2)	Not relevant	Not relevant	Kaplan and Volanakis (1974) Nunomura et al. (1990)
	↓			
	IEC	DEAE - cellulose	1.5 M NaCl	
	↓			
	IEC	DEAE - cellulose	NaCl & pH gradient	
7.	Precipitation with L - α – lecithin	Not relevant	Not relevant	Hokama et al. (1974)
	↓			
	Precipitation by dialysis against calcium chloride	Not relevant	Not relevant	
	↓			
	Precipitation with chloroform	Not relevant	Not relevant	
	↓			
	GF	Sephadex G - 200	Not relevant	
	↓			
	IEC	DEAE - cellulose	NaCl gradient	
8.	IEC	DEAE - cellulose (x2)	EDTA & NaCl	Johnson and Prellner (1977)
9.	AC	CPS – Sepharose	10 mM EDTA	de Beer et al. (1982)
	↓			
	GF	Ultrogel AcA44	Not relevant	
	↓			
	IAC	Anti NHS –Sepharose	Effluent used	
	↓			
	GF	Sephacryl S – 300	Not relevant	
10.	AC	Sepharose 4B	10 mM EDTA	de Beer and Pepys (1982)
	↓			
	IAC	Anti NHS – Sepharose	Effluent used	
	↓			
	AC	Blue Sepharose	Effluent used	
	↓			
	GF	Sephacryl S – 300	Not relevant	

(*continued on next page*)

Table 4 (*continued*)

S. No.	Methods of isolation	Matrix used*	Eluants used in adsorption chromatography	References
11.	AC	CH -Sepharose 4B	2 mM EGTA	Hashimoto and Tatsumi (1989)
	↓			
	HIC	Hydroxylapatite	Phosphate buffer gradient	
12.	IAC	Anti CRP - Sepharose 4B	1.5 M NaCl	Nunomura et al. (1990)
	↓			
	IEC	DEAE – Sephacel	500 mM NaCl	
13.	AC	Sepharose 4B	Effluent used	Köttgen et al. (1992)
	↓			
	AC	Phosphorylcholine - agarose	2 mM EDTA	
	↓			
	AC	Phosphorylcholine - agarose	1 mM phosphorylcholine	
14.	AC	Phosphorylcholine - Sepharose 4B	2 mM EDTA	Culley et al. (1996)
	↓			
	IEC	DEAE – cellulose	NaCl gradient	
	↓			
	GF	Sephacryl S – 300	Not relevant	
15.	AC	Agarose beads	Effluent used	Das et al. (2004)
	↓			
	AC	Phosphorylcholine - Sepharose 4B	10 mM EDTA	
	↓			
	AC	Phosphorylcholine - Sepharose 4B	2 mM phosphorylcholine	
2. Serum amyloid protein				
1.	Precipitation by dialysis against water	Not relevant	Not relevant	Binette et al. (1974)
	↓			
	GF	Biogel P – 300	Not relevant	
	↓			
	Preparative electrophoresis	Not relevant	Not relevant	
2.	AC	Sepharose 4B	50 mM sodium citrate	Pepys et al. (1977)
	↓			
	GF	Ultrogel AcA 34	Not relevant	
3.	Precipitation with barium chloride	Not relevant	Not relevant	Thompson and Enfield (1978)
	↓			
	Precipitation with ammonium sulphate (x2)	Not relevant	Not relevant	
	↓			
	GF	Sephadex G – 25	Not relevant	
	↓			
	IEC	DEAE - Sephadex G – 25	1 mM benzamidine in sodium citrate buffer gradient	
	↓			
	Precipitation with ammonium sulphate	Not relevant	Not relevant	
	↓			
	AC	Heparin-agarose	150 mM sodium citrate	

(*continued on next page*)

Table 4 (*continued*)

S. No.	Methods of isolation	Matrix used*	Eluants used in adsorption chromatography	References
4.	AC	Sepharose 4B	25 mM EDTA	Painter et al. (1982)
	↓			
	IEC	DEAE – cellulose	200 mM NaCl	
5.	AC	CPS - Sepharose 4B	10 mM EDTA	Hind et al. (1984)
	↓			
	GF	Ultrogel AcA44	Not relevant	
	↓			
	IAC	Mixture of Anti NHS - Sepharose 4B	Effluent used	
	↓	& Anti SAP - Sepharose 4B		
	AC	Blue Sepharose	Effluent used	
	↓			
	LAC	Con A – Sepharose	Effluent used	
	↓			
	GF	Sephacryl S – 300	Not relevant	
6.	AC	Biogel A - 0.5 m	10 mM EDTA	Potempa et al. (1985)
	↓			
	AC	Protein A - Sepharose CL - 4B	Effluent used	
	↓			
	GF	Ultrogel AcA34	Not relevant	
	↓			
	GF	Sephacryl S – 300	Not relevant	
7.	AC	Gelatin-Sepharose 4B	Effluent used	Hamazaki (1986)
	↓			
	AC	Lysine-Sepharose 4B	Effluent used	
	↓			
	AC	Glc - Gal - Hyl - CH Sepharose 4B	5 mM EDTA	
8	AC	Sepharose 4B	5 mM EDTA	Hamazaki (1987)
	↓			
	GF	TSK - GEL HW - 65S	Not relevant	
9.	AC	Phosphocholine - Sepharose 4B	Effluent used	Colley et al. (1988)
	↓			
	AC	Mannan - Sepharose CL - 4B	2 mM EDTA	
10.	Precipitation with calcium chloride (x2)	Not relevant	Not relevant	Urbányi and Medzihradszky (1992)
	↓			
	AC	Sepharose 6B	4 mM EDTA	
	↓			
	IEC	Sepabeads FP - DA05	NaCl gradient	
11.	AC	Sepharose CL - 4B	10 mM EDTA	Danielsen et al. (1997)
	↓			
	IEC	Mono – Q	NaCl gradient	
12.	Precipitation with ethanol	Not relevant	Not relevant	Kilpatrick (1997b)
	↓			
	Precipitation with ammonium sulphate	Not relevant	Not relevant	
	↓			
	AC	Emphaze - mannan (x2)	10 mM EDTA	

(*continued on next page*)

Table 4 (*continued*)

S. No.	Methods of isolation	Matrix used*	Eluants used in adsorption chromatography	References
3. H - Ficolin				
1.	Isoelectric precipitation	Not relevant	Not relevant	Yae et al. (1991)
	↓			
	HIC	Hydroxylapatite - Bio - Gel HTP	Phosphate buffer gradient	
	↓			
	Precipitation with ammonium sulphate	Not relevant	Not relevant	
	↓			
	GF	Sephadex G – 200	Not relevant	
	↓			
	Preparative electrophoresis	Not relevant	Not relevant	
	↓			
	LAC	Lentil lectin – agarose	200 mM α-methyl-D- mannoside	
	↓			
	IAC	Anti IgG - Sepharose 4B	Effluent used	
2.	IAC	Anti Hakata antigen - Sepharose 4B	Effluent used	Sugimoto et al. (1998)
	↓			
	IAC	Hitrap Protein G	Effluent used	
	↓			
	MAC	Zinc column	Glycine - HCl buffer gradient	
	↓			
	LAC	Lentil lectin – agarose	200 mM α -methyl - D - mannoside	
3.	Precipitation with ethanol	Not relevant	Not relevant	Matsushita et al. (2002)
	↓			
	Precipitation with polyethylene glycol	Not relevant	Not relevant	
	↓			
	AC	GlcNAc – agarose	Effluent used	
	↓			
	IAC	Anti H - Ficolin – Sepharose	100 mM glycine - HCl buffer	
	↓			
	LAC	Lentil - lectin – Sepharose	200 mM α - methyl - mannopyranoside	
	↓			
	IAC	Anti IgM – Sepharose	Effluent used	
	↓			
	AC	Protein A – Sepharose	Effluent used	
	↓			
	IAC	Anti MBL – Sepharose	Effluent used	
	↓			
	IAC	Anti L - Ficolin – Sepharose	Effluent used	
4. Mannan - binding lectin				
1.	AC	Mannan - Sepharose 4B (x3)	2mM EDTA	Kawasaki et al. (1983)
	↓			
	GF	Sepharose CL - 6B	Not relevant	

(*continued on next page*)

Table 4 (*continued*)

S. No.	Methods of isolation	Matrix used*	Eluants used in adsorption chromatography	References
2.	AC	Sepharose 4B	Effluent used	Summerfield and Taylor (1986)
	↓			
	AC	Mannan - Sepharose 4B	2 mM EDTA	
3.	AC	Reacti – gel	Effluent used	
	↓			
	AC	Mannan - Reacti – gel	2 mM EDTA	
	↓			
	AC	Mannan - oxirane acrylic beads	10 mM EDTA	
4.	AC	Mannan - Biogel P – 150	10 mM EDTA	Taylor and Summerfield (1987)
	↓			
	GF	Sepharose CL - 6B	Not relevant	
5.	AC	Phosphocholine - Sepharose CL - 4B	Effluent used	Colley et al. (1988)
	↓			
	AC	Mannan - Sepharose CL - 4B	2 mM EDTA	
	↓			
	AC	Mannan - Sepharose CL - 4B	50 mM mannose	
6.	GF	Sephacryl - S300	Not relevant	Super et al. (1989)
	↓			
	AC	Mannan – Sepharose	5 mM EDTA	
	↓			
	IAC	Anti IgM – Sepharose	Effluent used	
	↓			
	IEC	Mono – Q	1M NaCl	
7.	AC	Mannan - Sepharose	5 mM EDTA	
	↓			
	AC	Mannan – Sepharose	Mannose	
	↓			
	GF	Superose 6	Not relevant	
	↓			
	IEC	Mono – Q	1 M NaCl	
	↓			
	IAC	Anti IgM – Sepharose	Effluent used	
8.	AC	Mannan - Sepharose 4B	2 mM EDTA	Kuhlman et al. (1989)
	↓			
	AC	Mannan - Sepharose 4B	50 mM mannose	
9.	AC	Mannan - Sepharose 4B	10 mM EDTA	Lu et al. (1990)
	↓			
	AC	Mannan - Sepharose 4B	50 mM mannose	
	↓			
	GF	Superose 6 (HR10/30)	Not relevant	
	↓			
	IEC	Mono - Q (HR5/5)	NaCl gradient	
	↓			
	IAC	Anti IgM - Sepharose	Effluent used	

(*continued on next page*)

Table 4 (*continued*)

S. No.	Methods of isolation	Matrix used*	Eluants used in adsorption chromatography	References
10.	AC	Mannose - Sepharose 6B	10 mM EDTA	Kyogashima et al. (1990)
	↓			
	AC	Sepharose 6B	10 mM mannose	
11.	Precipitation with polyethylene glycol	Not relevant	Not relevant	Matsushita and Fujita (1992)
	↓			
	AC	Mannan - Sepharose 4B	300 mM mannose	
	↓			
	IAC	Anti IgM - Sepharose 4B	Effluent used	
	↓			
	IAC	Anti MBP - Sepharose 4B (x2)	100 mM glycine - HCl buffer	
12.	AC	Mannose - Sepharose 6B	10 mM EDTA	Terai et al. (1993)
	↓			
	AC	Sepharose 6B	50 mM mannose	
	↓			
	GF	Superose 6	Not relevant	
	↓			
	IEC	Mono – Q	NaCl gradient	
13.	Precipitation with polyethylene glycol	Not relevant	Not relevant	Tan et al. (1996)
	↓			
	AC	Mannose - Sepharose 4B	10 mM EDTA	
	↓			
	AC	Maltose - Sepharose 4B	100 mM N - acetylglucosamine	
	↓			
	IEC	Mono - Q (HR5/5)	NaCl gradient	
	↓			
	AC	Mannose-Sepharose 4B	10 mM EDTA	
	↓			
	GF	Superose 6	Not relevant	
14.	Precipitation with ethanol	Not relevant	Not relevant	Kilpatrick (1997a)
	↓			
	Precipitation with ammonium sulphate	Not relevant	Not relevant	
	↓			
	AC	Emphaze – mannan	10 mM EDTA	
	↓			
	AC	Emphaze – mannan	100 mM mannose	
15.	AC	Mannan - Sepharose 4B (x2)	20 mM EDTA	Suankratay et al. (1998)
	↓			
	AC	Protein A – Sepharose	Effluent used	
	↓			
	AC	Anti IgM – Sepharose	Effluent used	
16.	AC	Mannan - Sepharose 4B (x2)	20 mM EDTA	Saifuddin et al. (2000)
	↓			
	AC	Protein G – Sepharose	Effluent used	
	↓			
	IAC	Anti IgM – Sepharose	Effluent used	

(*continued on next page*)

Table 4 (*continued*)

S. No.	Methods of isolation	Matrix used*	Eluants used in adsorption chromatography	References
17.	Precipitation with polyethylene glycol	Not relevant	Not relevant	Matsushita et al. (2000)
	↓			
	AC	GlcNAc – agarose	300 mM mannose	
	↓			
	IAC	Anti MBL - Sepharose 4B	100 mM glycine - HCl buffer	
18.	Precipitation with polyethylene glycol	Not relevant	Not relevant	Muto et al. (2001)
	↓			
	AC	Mannan – agarose	10 mM EDTA	
	↓			
	AC	Mannan – agarose	50 mM mannose	
	↓			
	GF	Sephacryl S – 300	Not relevant	
	↓			
	IAC	Anti IgM – Sepharose	Effluent used	
	↓			
	AC	Protein G – Sepharose	Effluent used	
19.	Precipitation with ethanol	Not relevant	Not relevant	Neth et al. (2002)
	↓			
	Precipitation with ammonium sulphate	Not relevant	Not relevant	
	↓			
	AC	Mannan – agarose	10 mM EDTA	
	↓			
	AC	Mannan – agarose	100 mM mannose	
20.	AC	Mannose - Sepharose 4B	10 mM EDTA	Butler et al. (2002)
	↓ ↓			
	AC	Maltose - Sepharose 4B	100 mM N - acetylglucosamine	
	↓			
	GF	Sephacryl S – 300	Not relevant	
	↓			
	IAC	Anti α_2 - macroglobulin - Sepharose 4B	Effluent used	
21.	Precipitation with ethanol	Not relevant	Not relevant	Matsushita et al. (2002)
	↓			
	Precipitation with polyethylene glycol	Not relevant	Not relevant	
	↓			
	AC	GlcNAc – agarose	300 mM mannose	
	↓			
	IAC	Anti MBL - Sepharose 4B	100 mM glycine - HCl buffer	
22.	Precipitation with ethanol	Not relevant	Not relevant	Valdimarsson et al. (2003)
	↓			
	AC	Agarose	30 mM mannose	
	↓			
	IEC	Q-Sepharose	NaCl	
	↓			
	GF	Superose 6	Not relevant	

(*continued on next page*)

Table 4 (*continued*)

S. No.	Methods of isolation	Matrix used*	Eluants used in adsorption chromatography	References
23.	AC	Sepharose CL - 4B	30 mM mannose	Laursen, 2003
	↓			
	IEC	Q – Sepharose	NaCl	
	↓			
	GF	Superose 6	Not relevant	
24.	Precipitation with polyethylene glycol	Not relevant	Not relevant	Ma et al. (2004)
	↓			
	AC	Peptidoglycan - Sepharose 4B	300 mM mannose	
	↓			
	AC	Protein A - Sepharose CL - 4B	Effluent used	
	↓			
	IAC	Anti IgM - Sepharose 4B	Effluent used	
5. Tetranectin				
1.	Precipitation with barium citrate	Not relevant	Not relevant	Clemmensen et al. (1986)
	↓			
	AC	Lysine - Sepharose 4B	Effluent used	
	↓			
	Precipitation with ammonium sulphate	Not relevant	Not relevant	
	↓			
	AC	Plasminogen - Sepharose 4B	1 mM tranexamic acid	
	↓			
	IEC	DEAE - Sepharose CL - 6B	NaCl gradient	
	↓			
	GF	Ultrogel AcA34	Not relevant	
2.	Cryoprecipitate depletion	Not relevant	Not relevant	Fuhlendorff et al. (1987)
	↓			
	IAC	Antitetranectin - Sepharose 4B	3 M $MgCl_2$	
	↓			
	IAC	Antihuman plasma protein column	Effluent used	
	↓			
	GF	Ultrogel AcA34	Not relevant	
3.	AC	Hitrap Heparin - Sepharose	Phosphate buffer gradient	Thougaard et al. (2001)
6. L - Ficolin				
1.	Polyethylene glycol precipitation	Not relevant	Not relevant	Matsushita et al. (1996)
	↓			
	AC	Mannan - Sepharose 4B	150 mM N - acetylglucosamine	
	↓			
	IEC	Mono – Q	NaCl gradient	
2.	AC	Sepharose 4B	Effluent used	Le et al. (1997)
	↓			
	AC	GlcNAc - Sepharose 4B	100 mM N - acetylglucosamine	
	↓			
	IAC	Q - Sepharose 4B	Effluent used	
	↓			
	IEC	Mono – Q	NaCl gradient	
	↓			
	AC	Tris - blocked CNBr - activated Sepharose 4B	100 mM N - acetylglucosamine	

(*continued on next page*)

Table 4 (*continued*)

S. No.	Methods of isolation	Matrix used*	Eluants used in adsorption chromatography	References
3.	AC	Sepharose 4B	Effluent used	Le et al. (1998)
	↓			
	AC	GlcNAc - Sepharose 4B	200 mM N - acetylglucosamine	
	↓			
	IEC	Mono - Q (x2)	NaCl gradient	
	↓			
	AC	Tris - blocked CNBr - activated Sepharose 4B	200 mM N - acetylglucosamine	
4.	Precipitation with polyethylene glycol	Not relevant	Not relevant	Matsushita et al.,2000
	↓			
	AC	GlcNAc – agarose	150 mM N - acetylglucosamine	
	↓			
	IEC	Mono – Q	NaCl gradient	
	↓			
	AC	Anti MBL - Sepharose 4B	Effluent used	
5.	Precipitation with ethanol	Not relevant	Not relevant	Matsushita et al. (2002)
	↓			
	Precipitation with polyethylene glycol	Not relevant	Not relevant	
	↓			
	AC	GlcNAc – agarose	150 mM N - acetylglucosamine	
	↓			
	IEC	Mono – Q	NaCl gradient	
6.	Precipitation with ethanol	Not relevant	Not relevant	Cseh et al. (2002)
	↓			
	Precipitation with polyethylene glycol	Not relevant	Not relevant	
	↓			
	AC	GlcNAc – agarose	300 mM N - acetylglucosamine	
	↓			
	AC	Asialofetuin - Sepharose (x2)	300 mM N - acetylglucosamine	
	↓			
	IAC	Anti MBL - Sepharose 4B	Effluent used	
	↓			
	IAC	Anti H- ficolin - Sepharose 4B	Effluent used	
7.	Polyethylene glycol precipitation	Not relevant	Not relevant	Ma et al. (2004)
	↓			
	AC	1, 3 -β-D-glucan-Toyopearl	300 mM N - acetylglucosamine	
8.	Polyethylene glycol precipitation	Not relevant	Not relevant	Krarup et al. (2004)
	↓			
	AC	*N* - acetylcysteine - Sepharose CL - 4B	Lower ionic strength buffer	
	↓			
	IEC	Mono – Q	NaCl gradient	

Number given in parenthesis indicates the successive repetition of the same method employed.

Abbreviations used: AC = Affinity chromatography; CPS = Capsular polysaccharide; Con A = Concanavalin A; CNBr = Cyanogen bromide; CRP = C-reactive protein; DEAE = Diethylaminoethyl; EDTA = Ethylenediaminetetraacetic acid disodium salt; EGTA = Ethylene glycol -bis-(β - aminoethylether) *N, N, Ń, Ń* - tetraacetic acid; GF = Gel filtration; Glc-Gal-Hyl = 2-O-α-D-glucopyranosyl-O-β-D- galactopyranosyl hydroxylysine; HIC = Hydrophobic interaction chromatography; IAC = Immuno - affinity chromatography; IEC = Ion exchange chromatography; IgG = Immunoglobulin G; Immunoglobulin M = IgM; LAC = Lectin affinity chromatography; MAC = Metal affinity chromatography; MBL = Mannan-binding lectin; MBP = Mannan-binding protein; NHS = Normal human serum; SAP = Serum amyloid protein.

* The gel type of the matrix is given as reported by the investigators.

by SDS-PAGE under reducing conditions. As evident from these earlier investigations, different types of the isolated lectins showed considerable variations in their native molecular weight as well as subunit structures. Accordingly, the native molecular weight estimates for various lectins are: 118–140 kDa for C-reactive protein, 240–300 kDa for serum amyloid protein, 520–688 kDa for H-ficolin, 200–700 kDa for mannan-binding lectin, 68 or 90 kDa for tetranectin and 320 or 650 kDa for L-ficolin. The variations notable in these molecular weight estimates could be apparently due to the methods employed for both isolation of the lectins and estimation of their molecular mass. The analysis of subunit characteristics mostly by SDS-PAGE under reducing conditions revealed that various isolated lectin molecules are composed of identical subunits, but the number of subunits in different lectins varied between 3 and 22 and each subunit with molecular mass ranging from 20 to 40 kDa.

Table 5. Molecular characteristics of various lectins isolated from human blood (plasma/serum).

S. No.	Native molecular mass		Subunit characteristics*		References
	Method of estimation	kDa	Subunit molecular weight (kDa)	Number of subunits	
1. C-reactive protein					
1.	Analytical ultracentrifugation	118@	20/24@	6@	Gotschlich and Edelman (1965)
2.	Gel filtration	115–120	23		
				6	Kushner and Somerville (1970)
	Sucrose density gradient centrifugation	135–140			
3.	Gel filtration	120–140	Not tested	Not relevant	Siegel et al. (1974)
4.	Not tested	Not relevant	23	Not reported	Köttgen et al. (1992)
5.	Not tested	Not relevant	24	Not reported	Nunomura et al. (1990)
6.	Not tested	Not relevant	27–31	Not reported	Das et al. (2004)
2. Serum amyloid protein					
1.	Gel filtration	300	Not tested	Not relevant	Binette et al. (1974)
2.	Analytical ultracentrifugation	255.3	23/30	11/8	Painter et al. (1982)
3.	Polyacrylamide gradient gel electrophoresis	240	29.5	8	Hamazaki (1986)
4.	Polyacrylamide gradient gel electrophoresis	250	25	10	Hamazaki (1987)
5.	Gel filtration	255	25	10	Kubak et al. (1988)
6.	Not tested	Not relevant	25	Not reported	Hamazaki (1989)
7.	Polyacrylamide gradient gel electrophoresis	250	24	10	Urbányi and Medzihradszky (1992)
8.	Not tested	Not relevant	23	Not reported	Kilpatrick (1997b)
3. H - Ficolin					
1.	Gel filtration	650/688	35		
				~20	Yae et al. (1991)
	Analytical ultracentrifugation	520			
4. Mannan-binding lectin					
1.	Gel filtration	600	31	19	Kawasaki et al. (1983)
2.	Gel filtration	700 (MBP1)	32	22	Taylor and Summerfield (1987)
	Gel filtration	200 (MBP2)	28	7	
3.	Gel filtration	700	32	22	Super et al. (1989)
4.	Gel filtration	700	Not tested	Not relevant	Thiel et al. (1992)
5.	Gel filtration	400–700	Not tested	Not relevant	Matsushita and Fujita (1992)
6.	Not tested	Not relevant	32	Not reported	Terai et al. (1993)
7.	Not tested	Not relevant	32	Not reported	Tan et al. (1996)
8.	Not tested	Not relevant	28	Not reported	Kilpatrick (1997a)
9.	Not tested	Not relevant	31	Not reported	Butler et al. (2002)
10.	Not tested	Not relevant	30	Not reported	Ma et al. (2004)
5. Tetranectin					
1.	Gel filtration	68	17	4	Clemmensen et al. (1986)
2.	Gel filtration	80	Not tested	Not relevant	Clemmensen (1989)
3.	Gel filtration	90	30	3	Thougaard et al. (2001)
6. L - Ficolin					
1.	SDS-PAGE under non-reducing conditions	320	35	9	Matsushita et al. (1996)
2.	SDS-PAGE under non-reducing conditions	320			
			40	8	Le et al. (1997)
	Gel filtration	320			
3.	Gel filtration	650	35	18/19	Krarup et al. (2004)
		(oligomeric complex)			

@ CRP isolated from pooled pleural and peritoneal fluids and subunit characteristics examined by gel filtration and starch gel electrophoresis.
* Analysed by SDS-PAGE under reducing conditions.

1.15. Functions of humoral lectins

The six major types of humoral lectins have also been examined for their biological functions, especially their role in mediating various immune processes (Table 6). All the lectins, except H-ficolin, were reported to activate complement system as well as mediate opsonophagocytosis by macrophages and/or neutrophils. On the other hand, H-ficolin has been shown to activate complement system and inhibit bacterial growth. The latter functional feature implicates the ability of H-ficolin to interact directly with pathogenic bacteria and effectively abrogate their growth.

Table 6. A summary of literature pertaining to various immune functions demonstrated for the lectins naturally occurring in human blood (plasma/serum).

S. No.	Immune function	Action	References
1. C-Reactive protein			
1.	Phagocytic response of macrophages	Enhancement	Hokama et al. (1962); Ganrot and Kindmark (1969); Mortensen et al. (1976);
		(= Opsonophagocytosis)	Mortensen and Duskiewiez (1977); Zahedi et al. (1989); Culley et al. (1996)
2.	Phagocytic response of neutrophils	Enhancement	Kindmark (1971); Kilpatrick and Volanakis (1985); Kilpatrick et al. (1987);
		(= Opsonophagocytosis)	Edwards et al. (1982); Richardson et al. (1991); Mold et al. (2001)
3.	Lymphocyte blast transformation	Induction	Hornung and Fritchi (1971)
4.	Inhibition of growth of melanoma cells by	Enhancement	Hornung (1972)
	T-lymphocytes		
5.	Complement system	Activation	Kaplan and Volanakis (1974); Siegel et al. (1975); Claus et al. (1977);
			Volanakis (1982); Jiang et al. (1992); Gewurz et al. (1995);
			Wolbink et al. (1996); Szalai et al. (1999)
6.	Response of T lymphocytes to allogeneic cells	Inhibition	Mortensen et a1., 1975
7.	Antitumour activity of macrophages	Induction	Deodhar et al. (1982); Zahedi and Mortensen (1986);
			Zahedi et al. (1989); Tebo and Mortensen (1991)
8.	Colony formation of B lymphocytes	Modulation	Whisler et al. (1986)
9.	Complement activation by alternative pathway	Inhibition	Mold and Gewurz (1981); Mold et al. (1984)
10.	Respiratory burst in peripheral blood monocytes	Enhancement	Zeller et al. (1986)
11.	Migration of peritoneal macrophages	Inhibition	Miyagawa et al. (1989)
12.	Superoxide production and granule secretion by neutrophils	Inhibition	Buchta et al. (1988); Dobrinich and Spagnuolo (1991)
13.	Neutrophil chemotaxis	Inhibition	Kew et al. (2000); Zhong et al. (1998)
14.	Production of hydrogen peroxide by neutrophils	Induction	Tebo and Mortensen (1991)
15.	Production of pro - inflammatory cytokines from alveolar macrophages	Stimulation	Rochemonteix et al. (1993)
16.	MBL - initiated complement - mediated cytolysis	Inhibition	Suankratay et al. (1998)
17.	Complement activation by alternative pathway	Regulation	Mold et al. (1999)
2. Serum amyloid protein			
1.	C3b/C3bi - mediated phagocytosis by monocytes	Enhancement	Wright et al. (1983)
2.	Complement system	Activation	Bristow and Boackle (1986); Ying et al. (1993); Emsley et al. (1994)
3.	Factor I - mediated inactivation of C4b	Prevention	Schwalbe et al. (1992); Frutos et al. (1995)
3. Mannan-binding lectin			
1.	Phagocytic response of neutrophils	Enhancement	Miller et al. (1968); Soothill and Harvey (1976); Kuhlman et al. (1989);
		(= Opsonophagocytosis)	Malhotra et al. (1994); Turner (1996); Holmskov et al. (2003)
2.	Complement system	Activation	Ikeda et al. (1987); Lu et al. (1990); Yakota et al. (1995);
			Neth et al. (2002); Fujita et al. (2004)
3.	Phagocytic response of macrophages	Enhancement	Kuhlman et al. (1989); Turner (1996); Fraser et al. (1998);
		(= Opsonophagocytosis)	Tenner (1999); Kilpatrick (2002); Holmskov et al. (2003)
4.	Infection by human immunodeficiency virus	Inhibition	Ezekowitz et al. (1989)
5.	Neutrophil response against influenza A virus	Activation	Hartshorn et al. (1993); Malhotra et al. (1994)
6.	Complement - dependent cytotoxicity	Promotion	Ohta and Kawasaki (1994)
7.	Antitumour activity	Expression	Muto et al. (1999); Ma et al. (1999)
8.	Complement - independent cytotoxicity	Promotion	Ma et al. (1999)
9.	Neutralization of influenza A virus	Promotion	Anders et al. (1994); Kase et al. (1999)
10.	Release of cytokines by monocytes	Regulation	Jack et al. (2001)
11.	Phagocytic uptake of apoptotic cells by macrophages	Initiation	Ogden et al. (2001)
12.	Inflammatory reactions and immunity	Modulation	Turner (2003); Terai et al. (1997)
4. H - Ficolin			
1.	Complement system	Activation	Matsushita and Fujita. (2001); Matsushita et al. (2002); Lu et al. (2002)
2.	Growth of *Aerococcus viridians*	Inhibition	Tsujimura et al. (2001)
5. L - Ficolin			
1.	Phagocytic response	Enhancement	Matsushita et al. (1996); Lu et al. (2002)
	of neutrophils	(= Opsonophagocytosis)	
2.	Complement system	Activation	Matsushita et al. (2000); Matsushita and Fujita (2001); Matsushita et al. (2002)
			Lu et al. (2002); Lynch et al. (2004)

Table 7. Generation of diverse types of immunologically reactive molecules from various native biochemical constituents upon treatment with exogenous and endogenous substances.

[S. No.]	Source	Identity of target molecules	Treatment with exogenous/endogenous substances	Activity generated	References
1.	Bovine and human milk	Lactoferrin	Pepsin	Antibacterial	Bellamy et al. (1992)
2.	Hen eggs	Egg white lysozyme	Dimethyl suberimidate	Lectin-like	Mega and Hase (1994)
		Egg white lysozyme	Clostripain	Antibacterial	Pellegrini et al. (1997)
		Egg white lysozyme	Trypsin, chymotrypsin, pepsin	Antiviral	Overmann et al. (2003)
		Egg white lysozyme	Pepsin → trypsin	Antibacterial	Mine et al. (2004)
		Ovalbumin	Trypsin, chymotrypsin	Antibacterial	Pellegrini et al. (2004)
				Antifungal	
3.	Bovine milk	Casein	Trypsin, pronase,	Antibacterial	Zucht et al. (1995)
			endoproteinase Glu C		
4.	Bovine milk	Casein	Chymosin	Antibacterial	Lahov and Regelson, 1996
				Immunostimulatory	
5.	Bovine milk	β-lactoglobulin	Trypsin	Antibacterial	Pellegrini et al. (2001)
6.	Bovine serum	Albumin	Trypsin, chymotrypsin, pepsin	Antiviral	Overmann et al. (2003)
7.	Rabbit milk (*Oryctolagus cuniculus*)	Casein	Trypsin, chymotrypsin, pepsin, clostripain	Antibacterial	Baranyi et al. (2003)
8.	Human Serum	Human serum Albumin	Pronase	Hemagglutinating and Phenoloxidase activity	Beulaja and Manikandan (2012)

Table 8. Detection, Binding Specificity, Cation Dependency, Isolation, Molecular Characteristics and Immune function of a Pronase inducible lectin from human serum.

S. No.	Molecules Generated	Method of Detection	References
1.	Pronase inducible lectin	Hemagglutination	Beulaja and Manikandan (2012)
2.	Phenoloxidase	Oxidation of phenolic substrates	Beulaja and Manikandan (2012)

S. No.	Binding Specificity		Divalent Cation Dependency		References
	Ligands recognized	Best Ligand (s)	Cations tested	Dependency	
1.	Mannosamine, Glucosamine, Galactosamine	Mannosamine	Ca^{2+}, Mg^{2+}, Mn^{2+}, Sr^{2+}	Independent	Beulaja and Manikandan (2012), Beulaja et al. (2017)

S. No.	Methods of isolation	Matrix used	Eluants used in adsorption chromatography	References
1.	Lectin-Affinity Chromatography	Concanavalin A-Sepharose 4B	Mannose	Beulaja et al. (2017)

S. No.	Native molecular mass		Subunit characteristics		References
	Method of estimation	kDa	Subunit molecular weight (kDa)	Number of subunits	
1.	FPLC	6	3		
				2	Beulaja et al. (2017)
2.	MALDI-TOF	6.5			

S. No.	Immune function	Action	References
1.	Hemagglutination	Generation	Beulaja and Manikandan (2012)
2.	Phenoloxidase	Enhancement	Beulaja and Manikandan (2012)

1.16. Generation of defense molecules from native substances

The immune system utilizes naturally occurring defense molecules as well as synthesizes and releases certain specific molecules such as antibodies in order to accomplish effective immune reactions against the invaded pathogens. Apart from this well known aspect of humoral immune responses, the treatment of various native and non-immune biochemical constituents *in vitro* with different kinds of endogenous or exogenous substances has been found to result in generation of a variety of new immunologically relevant molecules. Such a phenomenon has attracted the attention of several researchers, apparently due to the fact that the generation of the defense molecules could augment the existing capacity of host immune responsiveness. A survey of the literature has been presented in Table 7. It is notable from these studies that the generation of immunologically reactive molecules appears to be a common phenomenon in vertebrates.

In vertebrates, many investigators have reported the generation of potent antibacterial or antiviral activity from lactoferrin (from bovine and human milk), casein (from bovine and ovine milk) and albumin (from bovine serum) upon treatment with various exogenous proteases (Table 7). Similarly, the treatment of egg white lysozyme and ovalbumin with such proteases has been found to generate antimicrobial activity. It is also interesting to note that lectin-like activity could also be generated from egg white lysozyme after chemical treatment (Mega and Hase, 1994).

As evident from the interesting findings of the novel experimental studies listed in Table 7, such investigations aimed at exploring the possibility for generation of immunologically reactive molecules need to be extended to human system. Although the presence of phenoloxidase (Bullón et al., 1998) and many distinct lectins (Table 1) have been detected in normal human serum, the generation of these new multifunctional defense molecules in human serum after treatment with appropriate elicitors. Based on these data, the objectives were framed wherein, *anew* pronase inducible lectin was detected, isolated and characterized, subsequently published and are included in the review table.

In Table 8, we have tabulated the generation and detection of hemagglutinating and phenoloxidase activities in human serum upon induction using an exogenous elicitor, namely pronase. The detected inducible lectin generated *anew* was successfully isolated by a single step using lectin-affinity chromatography with Concanavalin A- Sepharose as gel matrix. This lectin depicted specificity towards aminosugars, namely, mannosamine, glucosamine and galactosamine. This molecule has a native molecular weight of 6kDa and two sub units each of 3 kDa. Identification of the serum component involved in generation of neo-lectin with agglutinating and phenoloxidase activities in human serum was found to be human serum albumin (Beulaja et al., 2014) Further, exploration of study on this inducible lectin molecule or similar generations of such activities in human serum warrants further investigation.

Overall, it may be said that in this article, we have presented an explicit over view on the various human serum lectins and diverse activities that could be generated in vertebrates as review tables. We have discussed on various parameters like the mode of detection of human serum lectins, its isolation methodologies, structural and functional characteristics. In addition, we have tabulated our results on the pronase-inducible lectin isolated from human serum and its salient features. Over all this extensive review illustrates and demonstrates the massiveness of the enormous research work accomplished by eminent scientists worldwide on human serum lectins from 1930's till recent years.

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