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; Kanes, 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., 1993), 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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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 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        | Tillet and Francis (1930) |
|        | (Pentraxin)             |                      | Kushner and Somerville (1970) |
|        |                        | Radial immunodiffusion| Kaplan and Volanakis (1974) |
|        |                        | Capillary precipitin test | Di Camelli et al. (1980) |
|        |                        | Immunoelctrophoresis  | de Beer et al. (1982) |
|        |                        | Double immunodiffusion| Wadsworth et al. (1985) |
|        |                        | Nephelometry          | Wadsworth et al. (1985) |
|        |                        | Crossed immunoelctrophoresis | Wadsworth et al. (1985) |
|        |                        | Spot immunoprecipitate assay | Wadsworth et al. (1985) |
|        | Agglutination           |                      |             |
|        |                        | Heat-killed pneumococci| Tillet and Francis (1930) |
|        |                        | Pneumococcal capsular polysaccharide-coated sheep RBC | Gal and Milténý (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      | Shiné et al. (1981) |
|        |                        | Immunoradiometric assay | Shapiro and Shenkin (1989) |
|        |                        | Enzyme-linked immunosorbent assay | Nunomura et al. (1990) |
| 2.     | Serum amyloid protein   | Precipitation         | Cathcart et al. (1967) |
|        | (Pentraxin)             |                      | Pepys et al. (1977) |
|        |                        | Double immunodiffusion| Yae et al. (1991) |
|        |                        | Immunoelctrophoresis  | Sörensen et al. (1995) |
|        | Agglutination           |                      |             |
|        |                        | Complement-coated sheep RBC | Hutchcraft et al. (1981) |
|        |                        | Rat & horse RBC       | Hamazaki (1988) |
| 3.     | H-Ficolin               | Precipitation         | Inaba and Okochi (1978) |
|        | (Ficolin)               |                      | Yae et al. (1991) |
|        |                        | Double immunodiffusion| Yae et al. (1991) |
|        |                        | Immunoelctrophoresis  |             |
|        |                        | 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)             |                      | Summerfield and Taylor (1986) |
|        |                        | Enzyme-linked immunosorbent assay | Thiel et al. (1992) |
| 5.     | Tetranection            | Precipitation         | Clemmensen et al. (1986) |
|        |                        |                      |             |
|        |                        | Rocket immunoelctrophoresis |             |
|        |                        | Crossed immunoelctrophoresis |             |
|        |                        | Enzyme immunoassay (ELISA) | Thougaard et al. (2001) |
| 6.     | L-Ficolin               | N-acetylgalactosamine elution from affinity matrix | Matsushita et al. (1996) |
|        | (Ficolin)               |                      | Le et al. (1998) |
|        |                        | Enzyme-linked immunosorbent assay |             |
|        |                        | Time resolved fluorimetry | Krarup et al. (2004) |
et al., 1994; Arason, 1996). Lectins in mammalian systems have also been considered as key players of innate immunity and emerging as important components in the molecular mechanisms of invertebrates. Physiological functions such as removal of aged cells or modulation of internal host defence responses (Wang et al., 1998; Catalina et al., 1999; Ackerman et al., 1993; Wang et al., 1998). The actual physiological and immunological functions of many lectins remain to be precisely determined. However, in invertebrates their participation in various immuno-defense processes, namely, wound repair, clearance and opsono-phagocytosis of foreign targets are also well documented, 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), mannann-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 (mannann-binding lectin), ficolins (H- and L-ficolins) and tetranectin (Table 1).

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, 1967; 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 (Coome et al., 1984; Mullainathan and Renwantz, 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 Tillett & 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 immunoneutralisation 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 Matté, 1955), complement-coated sheep RBC (Hutchcroft 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.

| S. No. | Name of Lectin   | Concentration (μg/ml) | References | Site of Synthesis |
|--------|------------------|-----------------------|------------|-------------------|
| 1.     | C - reactive protein | 0.5–2                | Pepys and Baltz (1983) | Liver            |
|        |                   |                      | Dan 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          | Terni et al. (1993)     | Liver            |
|        |                   |                      | Summerfield and Taylor (1986) |              |
| 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) |                  |

Table 2. A profile of levels and site of synthesis of various lectins naturally occurring in human plasma/serum.
### Table 3. Binding specificity and divalent cation dependency of various lectins detected in human blood (plasma/serum) and other sources.

| S. No. | Binding Specificity | Best Ligand(s) | Cations tested | Dependency | References |
|--------|---------------------|----------------|----------------|------------|------------|
| 1.     | C-reactive protein (Source: serum/plasma, pleural, peritoneal or ascitic fluids) | | | | |
| 1.     | Precipitation assay | 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 N-acetylgalactosamine - phosphate | Not tested | Not relevant | Gotschlich and Liu (1967) |
| 4.     | Poly - L - lysine, poly - L - arginine, protamine sulphate, poly - L - ornithine | Protamine sulphate | Ca^{2+} | Not dependent | Di Camelli et al. (1980) |
| 5.     | Galactan | Galactan | Ca^{2+} | | Soelter and Uhlenbruck (1986) |
| 6.     | Inhibition of CRP - CPS precipitation assay | | | | |
| 7.     | L - α - Glycerophosphorylcholine | L - α - Glycerophosphorylcholine | Not tested | Not relevant | Kaplan and Volanakis (1974) |
| 8.     | Polybrene, phosphorylcholine, tetra - L - lysine | Polybrene | Not tested | Not relevant | Siegel et al. (1975) |
| 9.     | Glucosamine - 6 - phosphate | N - acetylgalactosamine - phosphate | Not tested | Not relevant | Gotschlich and Liu (1967) |
| 10.    | Phosphorylcholine | Phosphorylcholine | Not tested | Not relevant | Kaplan and Volanakis (1974) |
| 11.    | Complement activation | | | | |

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| S. No. | Binding Specificity | Best Ligand(s) | Divalent Cation Dependency | References |
|--------|---------------------|----------------|---------------------------|------------|
| 12.    | Protamine sulphate  | Protamine sulphate | Ca$^{2+}$ | Siegel et al. (1974) |
| 13.    | Protamine, poly-L-lysine, histone, myelin basic protein, poly-L-arginine | Protamine, poly-L-lysine, histone, myelin basic protein | Not tested | Siegel et al. (1975) |
| 14.    | Low density lipoprotein | Low density lipoprotein | Ca$^{2+}$ | de Beer et al. (1982) |
| 15.    | Fibronectin | Fibronectin | Ca$^{2+}$ | Salonen et al. (1984) |
| 16.    | Phosphorylcholine | β-D-Gal-(1-3)-D-GalNAc, with terminal galactose: (1-4) - D - GlcNAc | Not tested | Köttgen et al. (1992) |
| 17.    | Phosphorylcholine | Phosphorylcholine | Ca$^{2+}$ | Culley et al. (2000) |
| 18.    | Protein A from Streptococcus pyogenes | Protein A | Ca$^{2+}$ | Not dependent | Dax et al. (2004) |
| 19.    | Lipophosphoglycan | Lipophosphoglycan | Ca$^{2+}$ | Culley et al. (1996) |
| 20.    | Native and modified low density lipoprotein, cholesterol, Phosphorylcholine | Cholesterol, Phosphorylcholine | Ca$^{2+}$ | Tarkinen et al. (2002) |

2. Serum amyloid protein (Source: plasma/serum or ascitic fluid)

## Solid phase direct binding assay

| S. No. | Binding Specificity | Best Ligand(s) | Divalent Cation Dependency | References |
|--------|---------------------|----------------|---------------------------|------------|
| 1.     | Agarose, agar, sulphated polyacrylamide | Agarose | Ca$^{2+}$ | Pepys et al. (1977) |
| 2.     | Heparin, agarose | Heparin | Ca$^{2+}$ | Thompson and Enfield (1978) |
| 3.     | Cyclic and non-cyclic 4, 6 pyruvate acetal of galactose | Cyclic 4, 6 pyruvate acetal of galactose | Ca$^{2+}$ | Hind et al. (1984) |
| S. No. | Binding Specificity | Ligands recognized | Best Ligand (s) | Cations tested | Dependency | References |
|-------|---------------------|--------------------|----------------|---------------|------------|------------|
| 4.    | Fibronectin, C4 - binding protein | Not reported | Ca²⁺ | Ca²⁺ | | de Beer et al. (1981) |
| 5.    | DNA, chromatin | DNA | Ca²⁺ | Ca²⁺ | | Pepys and Butler (1987) |
| 6.    | C4 - binding protein | C4 - binding protein | Ca²⁺ | Ca²⁺ | | Frutos et al. (1995) |
| 7.    | Laminin | Laminin | Ca²⁺, Mg²⁺, Mn²⁺, Zn²⁺ | Ca²⁺ | | Zahedi (1997) |
| 8.    | Agglutination of complement - coated sheep RBC | C3b | Ca²⁺ | Ca²⁺ | | Hutchcraft et al. (1981) |
| 9.    | Radiolabelled fluid phase binding assay | Zymosan | Ca²⁺, Cu²⁺, Mg²⁺, Mn²⁺, Ni²⁺, Zn²⁺, Cd²⁺, Ba²⁺, Co²⁺, Zn²⁺ | Ca²⁺, Cu²⁺, Cd²⁺, Cu²⁺, Cd²⁺, Zn²⁺ | | Potempa et al. (1985) |
| 10.   | Inhibition of radiolabelled lectin binding assay | Galactose | Ca²⁺, Mg²⁺ | Ca²⁺ | | Hamazaki (1986) |
| 11.   | Inhibition of rabbit RBC agglutination | Simple substances: | Not tested | Not relevant | | |
|       | Non - acetylated and N – acetylated 2 - O - α - D - glucopyranosyl - O - β - D - galactopyranosyl hydroxylysine Stachyose | | Not tested | Not relevant | | |
|       | Glycoconjugates: | Orosomucoid, desialylated orosomucoid, human glycophorin | Not tested | Not relevant | | |
|       | Desialylated glycophorin | Desialylated bovine erythrocyte glycoprotein | Not tested | Not relevant | | |
|       | Bovine erythrocyte glycoprotein | | | | |
|       | Desialylated bovine erythrocyte | | | | |
|       | Glycoprotein | | | | |
| 12.   | Radiolabelled ligand binding and inhibition assays | Glycosaminoglycans: | | | | |
|       | Heparan, dermatan sulphate, Heparin | Heparin | Ca²⁺, Ba²⁺, Cd²⁺, Cu²⁺ | Ca²⁺, Cd²⁺ | | Hamazaki (1987) |
|       | Heparin, chondroitin - 4 - sulphate, Chondroitin - 6 - sulphate | | Mg²⁺, Mn²⁺, Sr²⁺, Zn²⁺ | | | |
|       | 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 | | | | | |
| 14.   | Inhibition of rabbit RBC agglutination | Dermatan sulphate | Hyaluronic acid | Not tested | Not relevant | |
|       | Heparan sulphate | | | | | |
|       | Hyaluronic acid | | | | | |
Table 3 (continued)

| S. No. | Binding Specificity                                      | Best Ligand (s) | Divalent Cation Dependency | References |
|--------|----------------------------------------------------------|-----------------|-----------------------------|------------|
|        | **Enzyme - linked fluorescent immunoassay**             |                 |                             |            |
| 15.    | Zymosan, ovalbumin, porcine thyroglobulin C3bi, β-glucuronidase | Zymosan         | Ca²⁺                        | Kubak et al. (1988) |
| 16.    | Heparin, heparan sulphate, Dextran sulphate              | Dextran sulphate | Not tested                  | Hamazaki (1989) |
| 17.    | Heparin, heparan sulphate, Dextran sulphate              | Heparin, Dextran sulphate | Ca²⁺                        | Danielsen et al. (1997) |
|        | **H-Ficolin (Source: serum/plasma)**                     |                 |                             |            |
| 1.     | Solid phase direct binding assay                         | N-acetylgalactosamine | N-acetylgalactosamine       | Sugimoto et al. (1998) |
| 2.     | Agglutination of LPS - sensitised human O RBC            | LPS from Salmonella typhimurium | Ca²⁺                        |            |
|        | **Mannan - binding lectin (Source: serum/plasma)**      |                 |                             |            |
| 1.     | Inhibition of radiolabelled ligand binding assay         | N-acetylmannosamine | N-acetylmannosamine         | Kawasaki et al. (1983) |
| 2.     | Electroblot analysis                                    | D-glucose, D-galactose | Invertase, mannan           | Summerfield and Taylor (1986) |
|        | **MBP1: N-acetylgalactosamine**                          |                 |                             |            |
|        | **MBP2: N-acetylmannosamine, mannose, fucose, glucose, mannan, invertase, orosomucoid** |                 |                             |            |

(continued on next page)
Table 3 (continued)

| S. No. | Binding Specificity | Best Ligand(s) | Divalent Cation Dependency | References |
|--------|---------------------|----------------|---------------------------|------------|
| 4.     | Phospholipids:      | Phosphatidylinositol | Not tested | Not relevant | Kilpatrick (1998) |
|        | Phosphatidylserine  |                |                           |            |
|        | Phosphatidylinositol |                |                           |            |
|        | Phosphatidylcholine  |                |                           |            |
|        | Complement activation |            |                           |            |
| 5.     | Zymosan             | Zymosan        | Ca$^{2+}$                 |            |
|        | Enzyme - linked lectin immunosorbent assay | | | Lu et al. (1990) |
| 6.     | Mannose, N-acetylgalactosamine, N-acetylgalactosamine | Mannose, N-acetylgalactosamine | Ca$^{2+}$ | Ca$^{2+}$ | Thiel et al., 1992 |
|        | Enzyme - linked lectin binding assay | | | | |
| 7.     | Mannose, glucose, L-fucose, maltose, N-acetylmannosamine, N-acetylgalactosamine | N-acetylgalactosamine | Ca$^{2+}$ | Ca$^{2+}$ | Haurum et al. (1993) |
|        | Inhibition of phospholipid binding assay | | | | |
| 8.     | Mannose, fucose, glucose, m-inositol, maltose, N-acetylmannosamine, N-acetylgalactosamine | N-acetylgalactosamine | Not tested | Not relevant | Kilpatrick (1998) |
|        | Enzyme - linked lectin binding assay | | | | |
| 5.     | Serum/amniotic fluid |            |                           |            |
| 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) |
| 5.     | Ligand blot analysis |            |                           |            |
|        | Plasminogen         | Plasminogen    | Not tested | Not relevant | Westergaard et al. (2003) |
|        | Hepatocyte growth factor | | | | |
|        | Tissue type plasminogen | | | | |
|        | Urokinase type plasminogen | | | | |
|        | Prothrombin         |                |                           |            |
| 6.     | Ficolin (Source: serum/plasma) | Dot blot with radiolabelled lectin/solid phase direct binding assay | | | |
| 1.     | N-acetylgalactosamine | Not reported | Ca$^{2+}$ | Ca$^{2+}$ | Matsushita et al. (1996) |
|        | Asialofetuin        |                |                           |            |
|        | Elution from affinity gel matrix | | | | |
| 2.     | N-acetylgalactosamine | N-acetylgalactosamine | Ca$^{2+}$ | Not dependent | Le et al. (1997) |
| 3.     | N-acetylgalactosamine | Not reported | Not tested | Not relevant | Le et al. (1998) |
|        | N-acetylgalactosamine | | | | |
|        | Glutathione         |                |                           |            |
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-acetylglactosamine, mannan, plasminogen and N-acetylgalactosamine 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 Enfeld, 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) |
| 2.     | 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 |             |
|        | Precipitation with ammonium sulphate | Not relevant | Not relevant |             |
|        | Gel adsorption       | Reinagar    | 10 mM EDTA                               |             |
| 2.     | Precipitation with barium sulphate | Not relevant | Not relevant | Ganrot and Kindmark (1969) |
|        | Precipitation with ammonium sulphate | Not relevant | Not relevant |             |
|        | GF Sephadex G - 200  | Not relevant | 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) |
|        | Precipitation with ammonium sulphate (x2) | Not relevant | Not relevant | Kaplan and Volanakis (1974) |
|        | GF Sephadex G - 200  | Not relevant | Not relevant | Nunomura et al. (1990) |
| 6.     | Precipitation with ammonium sulphate (x2) | Not relevant | Not relevant | Hokama et al. (1974) |
|        | IEC DEAE - cellulose | Not relevant | 1.5 M NaCl                               |             |
|        | IEC DEAE - cellulose | Not relevant | NaCl & pH gradient                       |             |
| 7.     | Precipitation with L-α - lecithin | Not relevant | Not relevant |             |
|        | Precipitation with dialysis against calcium chloride | Not relevant | Not relevant | Hokama et al. (1974) |
|        | Precipitation with chloroform | Not relevant | Not relevant |             |
|        | GF Sephadex G - 200  | Not relevant | Not relevant |             |
|        | IEC DEAE - cellulose | Not relevant | NaCl gradient                            |             |
| 8.     | IEC DEAE - cellulose (x2) | Not relevant | EDTA & NaCl                             | Johnson and Prellner (1977) |
| 9.     | AC CPS – Sepharose | Not relevant | 10 mM EDTA                               | de Beer et al. (1982) |
|        | GF Ulgroel AcA44    | Not relevant | Effluent used                           |             |
|        | IAC Anti NHS - Sepharose | Not relevant | Effluent used                          |             |
| 10.    | AC Sephacryl S – 300 | Not relevant | 10 mM EDTA                               | de Beer and Pepys (1982) |
|        | AC Blue Sepharose   | Effluent used | Effluent used                           |             |
| 10.    | GF Sephacryl S – 300 | Effluent used | Effluent used                           |             |

(continued on next page)
| 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) |
| 12.   | IAC                  | Anti CRP-Sepharose 4B | 1.5 M NaCl | Ninomura et al. (1990) |
| 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-Sepharose 4B | NaCl gradient | |
|       | GF                   | Sephacryl S-300 | Not relevant | Das et al. (2004) |
|       | AC                   | Agarose beads | Effluent used | |
|       | 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
   - Rinette et al. (1974)

2. AC
   - Sepharose 4B
   - 50 mM sodium citrate
   - Pepys et al. (1977)

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
| 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                           |            |
|       | 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) |
|       | 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                              | Hamazaki (1987) |
| 8.    | AC                   | Sepharose 4B| 5 mM EDTA                               |            |
|       | 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                        |            |
| S. No. | Methods of isolation       | Matrix used | Eluants used in adsorption chromatography | References                  |
|-------|---------------------------|-------------|-------------------------------------------|-----------------------------|
| 3. H - Ficolin |                          |             |                                           |                             |
| 1.    | Ioelectric 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                             | Sugimoto et al. (1998)     |
| 2.    | IAC                       | Anti Hakata antigen - Sepharose 4B | Effluent used |                             |
|       | 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                              | Matsuhashi 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) |
|        |                      |             |                                          |            |
| 3.     | AC                   | Mannan - Sepharose 4B | 2 mM EDTA | Summerfield and Taylor (1986) |
|        |                      |             |                                          |            |
| 4.     | AC                   | Mannan - oxirane acrylic beads | 10 mM EDTA | Summerfield and Taylor (1986) |
|        |                      |             |                                          |            |
| 5.     | AC                   | Sepharose CL - 6B | Not relevant | Super et al. (1989) |
|        |                      |             |                                          |            |
| 6.     | AC                   | Mannan - Sepharose | 5 mM EDTA | Super et al. (1989) |
|        |                      |             |                                          |            |
| 7.     | AC                   | Sephaeryl - S300 | Effluent used | Super et al. (1989) |
|        |                      |             |                                          |            |
| 8.     | AC                   | Mannan - Sepharose 4B | 2 mM EDTA | Kuhlman et al. (1989) |
|        |                      |             |                                          |            |
| 9.     | AC                   | Mannan - Sepharose 4B | 10 mM EDTA | Lu et al. (1990) |
|        |                      |             |                                          |            |
| 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)                 |            |
|       | ↓                                    |             |                                          |            |
| 11.   | 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 (x2)       | 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 |                                          |            |
| 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                  | Anit 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 |             |
|       | IAC                  | Mannan – agarose | 50 mM mannose |             |
|       | GF                   | Sephacryl S – 300 | Not relevant |             |
|       | IAC                  | Anit IgM – Sepharose | Effluent used |             |
|       | AC                   | Protein G – Sepharose | Effluent used |             |
| 19.   | Precipitation with ethanol | Not relevant | Not relevant | Neth et al. (2002) |
|       | AC                   | Mannan – agarose | 10 mM EDTA |             |
|       | AC                   | Mannan – agarose | 100 mM mannose |             |
| 20.   | AC                   | Mannanose - Sepharose 4B | 10 mM EDTA | Butler et al. (2002) |
|       | AC                   | Maltose - Sepharose 4B | 100 mM N - acetylglucosamine |             |
|       | GF                   | Sephacryl S – 300 | Not relevant |             |
|       | IAC                  | Anit α2 - macroglobulin - Sepharose 4B | Effluent used |             |
| 21.   | Precipitation with ethanol | Not relevant | Not relevant | Matsushita et al. (2002) |
|       | AC                   | GlcNAc – agarose | 300 mM mannose |             |
|       | IAC                  | Anit 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)
| S. No. | Methods of isolation | Matrix used | Eluants used in adsorption chromatography | References |
|--------|---------------------|-------------|------------------------------------------|------------|
| 23.    | AC                  | Sepharose CL - 4B | 30 mM mannose | Laursen, 2003 |
|        |                     | IEC         | NaCl | | |
|        |                     | GF          | Not relevant | | |
| 24.    | Precipitation with polyethylene glycol | Not relevant | Not relevant | Ma et al. (2004) |
|        |                     | AC          | Peptidoglycan - Sepharose 4B | 300 mM mannose |
|        |                     | IAC         | Anti IgM - Sepharose 4B | Effluent used |
|        |                     | GF          | Ultrogel AcA34 | Not relevant |
| 5.     | Tetranectin         |             |                          |            |
| 1.     | Precipitation with barium citrate | Not relevant | Not relevant | Clemmensen et al. (1986) |
|        |                     | AC          | Lysine - Sepharose 4B | Effluent used |
|        |                     | IAC         | Antitetranectin - Sepharose 4B | 3 M MgCl₂ |
|        |                     | GF          | Ultrogel AcA34 | Not relevant |
| 2.     | Cryoprecipitate depletion | Not relevant | Not relevant | Fuhlendorff et al. (1987) |
|        |                     | 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) |
|        |                     | IAC         | GlcNAc - Sepharose 4B | 100 mM N - acetylglucosamine |
|        |                     | IEC         | Q - Sepharose 4B | Effluent used |
|        |                     | IEC         | Mono – Q | NaCl gradient |
|        |                     | AC          | Tris - blocked CNBr - activated Sepharose 4B | 100 mM N - acetylglucosamine |
| S. No. | Methods of isolation | Matrix used[^2] | Eluants used in adsorption chromatography | References |
|-------|---------------------|-----------------|------------------------------------------|-------------|
| 3.    | AC                  | Sepharose 4B    | Effluent used                            | Le et al. (1998) |
|       |                     | GlcNAc-Sepharose 4B | 200 mM N-acetylglucosamine           |             |
|       |                     | 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 |
|       |                     | GlcNAc-agarose | 150 mM N-acetylglucosamine |             |
|       |                     | Mono - Q NaCl gradient |                          |             |
| 5.    | Precipitation with ethanol | Not relevant | Not relevant | Matsushita et al. (2002) |
|       |                     | GlcNAc-agarose | 150 mM N-acetylglucosamine |             |
|       |                     | Mono - Q NaCl gradient |                          |             |
| 6.    | Precipitation with ethanol | Not relevant | Not relevant | Cseh et al. (2002) |
|       |                     | GlcNAc-agarose | 300 mM N-acetylglucosamine |             |
|       |                     | Anti MBL-Sepharose 4B | Effluent used |             |
|       |                     | Anti H-ficolin-Sepharose 4B | Effluent used |             |
| 7.    | Polyethylene glycol precipitation | Not relevant | Not relevant | Ma et al. (2004) |
|       |                     | 1, 3-β-D-glucan-Toyopearl | 300 mM N-acetylglucosamine |             |
| 8.    | Polyethylene glycol precipitation | Not relevant | Not relevant | Kranup et al. (2004) |
|       |                     | N-acetylcysteine-Sepharose CL-4B | Lower ionic strength buffer |             |
|       |                     | 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-aminoethyl ether) N, N, N, N-tetraacetic acid; GF = Gel filtration; Glc-Gal-Hyl = 2-O-α-D-glucopyranosyl-O-β-D-galactopyranosyl hydroxylysine; HIC = Hydrophobic interaction chromatography; IAC = Immunoaffinity 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.

[^2]: 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 tetranection 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 | Method of estimation | Subunit molecular weight | Subunit characteristics | References |
|-------|-----------------------|----------------------|-------------------------|------------------------|------------|
| 1. C-reactive protein | 118–140 kDa | Analytical ultracentrifugation | 20/24 | 6 | Gotschlich and Edelman (1965) |
| 2. | Gel filtration | 115–120 | 23 | 6 | Kushner and Somerville (1970) |
| 3. | Sucrose density gradient centrifugation | 135–140 | Not tested | Not relevant | Siegel et al. (1974) |
| 4. | Not tested | Not tested | Not relevant | Not reported | Kötgen et al. (1992) |
| 5. | Not tested | Not tested | 24 | Not reported | Nunomura et al. (1990) |
| 6. | Not tested | Not relevant | 27–31 | Not reported | Das et al. (2004) |
| 2. Serum amyloid protein | 300 | Gel filtration | Not tested | Not relevant | Binette et al. (1974) |
| 3. | Analytical ultracentrifugation | 255.3 | 23/30 | 11/8 | Painter et al. (1982) |
| 4. | Polyacrylamide gradient gel electrophoresis | 240 | 29.5 | 8 | Hamazaki (1986) |
| 5. | Polyacrylamide gradient gel electrophoresis | 250 | 25 | 10 | Hamazaki (1987) |
| 6. | Gel filtration | 255 | 25 | 10 | Kubak et al. (1988) |
| 7. | Not tested | Not relevant | 25 | Not reported | Hamazaki (1989) |
| 8. | Polyacrylamide gradient gel electrophoresis | 250 | 24 | 10 | Urbaný and Medzihradsky (1992) |
| 9. | Not tested | Not relevant | 23 | Not reported | Kilpatrick (1997b) |
| 2. H - Ficolin | 650/688 | Gel filtration | 35 | –20 | Yae et al. (1991) |
| 1. | Analytical ultracentrifugation | 520 | | | |
| 4. Mannan-binding lectin | 600 | Gel filtration | 31 | 19 | Kawazaki et al. (1983) |
| 2. | Gel filtration | 700 (MBP1) | 32 | 22 | Taylor and Summerfield (1987) |
| 3. | Gel filtration | 200 (MBP2) | 28 | 7 | |
| 4. | Gel filtration | 700 | 32 | 22 | Super et al. (1989) |
| 5. | Gel filtration | 700 | Not tested | Not relevant | Thiel et al. (1992) |
| 6. | Gel filtration | 400–700 | Not tested | Not relevant | Matsushita and Fujita (1992) |
| 7. | Not tested | Not relevant | 32 | Not reported | Terai et al. (1993) |
| 8. | Not tested | Not relevant | 32 | Not reported | Tan et al. (1996) |
| 9. | Not tested | Not relevant | 28 | Not reported | Kilpatrick (1997a) |
| 10. | Not tested | Not relevant | 31 | Not reported | Butler et al. (2002) |
| 11. | Not tested | Not relevant | 30 | Not reported | Ma et al. (2004) |
| 5. Tetranection | 68 | Gel filtration | 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 | 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) |
| 3. | Gel filtration | 320 | | | |
| 4. | Gel filtration | 650 | 35 | 18/19 | Krarup et al. (2004) |

* 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 | Enhancement | Hokama et al. (1962); Ganrot and Kindmark (1969); Mortensen et al. (1976); Mortensen and Duskiewiez (1977); Zahedi et al. (1989); Culley et al. (1996); 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); 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 T-lymphocytes | Enhancement | Hornung (1972) |
| 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); Volanakis (1982); Jiang et al. (1992); Gewurz et al. (1995); Volanakis (1982); Jiang et al. (1992); Gewurz et al. (1995) |
| 6. | Response of T lymphocytes to allogeneic cells | Inhibition | Mortensen et al., 1975 |
| 7. | Antitumour activity of macrophages | Induction | Deodhar et al. (1982); Zahedi and Mortensen (1986); Zahedi and Mortensen (1986); Tebo and Mortensen (1991) |
| 8. | Colony formation of B lymphocytes | Modulation | Whisler et al. (1986) |
| 9. | Respiratory burst in peripheral blood monocytes | Enhancement | Zeller et al. (1986) |
| 10. | Migration of peritoneal macrophages | Enhancement | Miyazawa et al. (1989) |
| 11. | Superoxide production and granule secretion by neutrophils | Inhibition | Bachta et al. (1988); Dohring and Spagnuolo (1991) |
| 12. | Neutrophil chemotaxis | Inhibition | Kew et al. (1986); Zhong et al. (1998) |
| 13. | Production of hydrogen peroxide by neutrophils | Induction | Tebo and Mortensen (1991) |
| 14. | Production of pro-inflammatory cytokines from alveolar macrophages | Stimulation | Rochmentteix et al. (1993) |
| 15. | MBL-initiated complement-mediated cytolysis | Inhibition | Suankratay et al. (1998) |
| 16. | Complement activation by alternative pathway | Regulation | Mold et al. (1999) |

2. Serum amyloid protein

| S. No. | Immune function | Action | References |
|-------|----------------|--------|------------|
| 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

| S. No. | Immune function | Action | References |
|-------|----------------|--------|------------|
| 1. | Phagocytic response of neutrophils | Enhancement | Miller et al. (1968); Sotoho and Harvey (1976); Kuhlman et al. (1989); Malhotra et al. (1994); Turner (1996); Holmsoe et al. (2003) |
| 2. | Complement system | Activation | Ikeda et al. (1987); Lu et al. (1990); Yakota et al. (1993); Neth et al. (2002); Fujita et al. (2004) |
| 3. | Phagocytic response of macrophages | Enhancement | Kuhlman et al. (1989); Turner (1996); Holmsoe 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 | Ohita and Kawasaki (1994) |
| 7. | Antitumour activity | Expression | Muto et al. (1999); Ma et al. (1999) |
| 8. | Complement-independent cytotoxicity | Promotion | Andersen et al. (1994); Kase et al. (1999) |
| 9. | Release of cytokines by monocytes | Regulation | Jack et al. (2001) |
| 10. | Phagocytic uptake of apoptotic cells by macrophages | Initiation | Ogden et al. (2001) |
| 11. | Inflammatory reactions and immunity | Modulation | Turner (2003); Terai et al. (1997) |

4. H-ficolin

| S. No. | Immune function | Action | References |
|-------|----------------|--------|------------|
| 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

| S. No. | Immune function | Action | References |
|-------|----------------|--------|------------|
| 1. | Phagocytic response of neutrophils | Enhancement | Matsushita et al. (1996); Lu et al. (2002) |
| 2. | Complement system | Activation | Matsushita et al. (2002); Matsushita and Fujita (2001); Matsushita et al. (2002) |
|      | of neutrophils | (= Opsonophagocytosis) | Matsushita 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) |
| 3.     | Bovine milk | Casein | Trypsin, pronase, endoproteinase Glu C | Antibacterial | Zucht et al. (1995) |
| 4.     | Bovine milk | Casein | Chymosin | Antibacterial | Lahov and Regelson, 1996 |
|        |         | β-lactoglobulin | Trypsin | Antiviral | 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 | Borny 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 |
|--------|--------------------|---------------------------|------------|
| 1.     | Mannosamine, Glucosamine, Galactosamine | Ca²⁺, Mg²⁺, Mn²⁺, Sr²⁺ | 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 | kDa | Subunit characteristics | Subunit molecular weight (kDa) | Number of subunits | References |
|--------|-----------------------|-----|-------------------------|-----------------------------|-----------------|------------|
| 1.     | FPLC                  | 6   | 3                       |                             |                 | Beulaja et al. (2017) |
| 2.     | MALDI-TOF             | 6.5 |                         |                             | 2               | Beulaja et al. (2017) |

| 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 anti-bodies in order to accomplish effective immune reactions against the invaded pathogens. Apart from this well known aspect of humoral im-mune 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), caerin (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, new 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 generation 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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