Modulation of Innate and Adaptive Immune Responses by Arabinoxylans

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Abstract

Humans are exposed to harmful pathogens and a wide range of noxious substances every day. The immune system reacts to, and destroys, these pathogens and harmful substances. The immune system is composed of innate and adaptive immunity, which liaise to protect the host and maintain health. Foods, especially cereals, have been reported to modulate the immune response. Arabinoxylans are non-starch polysaccharides that have been shown to possess immune-modulatory activities. This review article discusses the fundamentals of the immune system and provides an overview of the immunomodulatory potential of arabinoxylans in conjunction with their structural characteristics and proposed similarities with lipopolysaccharides.

Practical applications

Understanding how the immune system works is of vital importance to prevent unnecessary or excessive inflammatory responses. Consumption of arabinoxylans has been shown to possess immunomodulatory potential. However, their mechanism of action has not been elucidated. Arabinoxylans share some similarities with lipopolysaccharides (LPS), a molecule that induces substantial and sometimes excessive immune responses such as fever following infection by pathogens. Thus, we propose that arabinoxylans might possibly act on the same receptor as LPS. Competition between dietary-derived arabinoxylans and LPS at a shared receptor would then have the potential to inhibit or attenuate excessive LPS-induced inflammatory responses that are typical of infection/fever. In the absence of infection and consequently no competition at the LPS receptor, consumption of dietary arabinoxylans may protect against the risk of infection by moderately activating the receptor and heightening natural (background) levels of immunity.

Keywords: Arabinoxylans, lipopolysaccharides, innate immunity, adaptive immunity, nitric oxide, Toll-like receptor

1. Introduction

The human body is continually exposed to pathogens or harmful agents. The immune system possesses a set of defence mechanisms against these harmful pathogens and is composed of innate (non-specific) and adaptive (specific) immunity (Nicholson, 2016). The innate immunity encompasses chemical, microbiological and physical barriers, in addition to other elements of the immune system such as monocytes, macrophages, neutrophils, the complement system and cytokines (Sperandio et al., 2015). The innate response is immediate and non-specific, unlike the adaptive immunity, which is considered the hallmark of the immune system with its specific, yet slower response (Iwasaki & Pillai, 2014; Iwasaki & Medzhitov, 2015). Mounting an immune response against harmless foreign molecules is unnecessary and can lead to fatal outcomes such as anaphylactic shock (Patosuo, 2014). This deleterious response is typically avoided because the adaptive immune response is triggered by the innate immune system only when the latter recognises molecules of an attacking pathogen (Bonneaud et al., 2003; Lu et al., 2016).

Performance of the immune system is vital for defending the body from pathogens and it plays a crucial role in health homoeostasis (Nairz et al., 2013). It has been suggested that ingestion of foods with immune-modulatory effects is able to prevent deterioration of immune function or reduce the risk of infection (Kaminogawa & Nanno, 2004; Goldsmith & Sartor, 2014). Studies have suggested that diet can improve depressed immune function by moderating the severity of infectious diseases and reducing infection rates (El-Gamal et al., 2011; Rajilić-Stojanović et al., 2015). Cereals are staple foods and feed more than half of the world's population; they are composed mainly of starch, protein, some minerals, and non-starch

78 polysaccharides that cannot be digested by human enzymes (Mohan et al., 2010). Arabinoxylan
79 is the main non-starch polysaccharide of many cereals (Zhou et al., 2010; Lovegrove et al.,
80 2017). It has been reported that arabinoxylan possesses immune-modulatory effects (Li et al.,
81 2015). Moreover, there is a structural similarity between arabinoxylans and the
82 lipopolysaccharides of Gram-negative bacteria (Park et al., 2009; Park et al., 2017). The aim
83 of this review is to give an overview of the immune system and how arabinoxylans might
84 modulate the immune response.

85

2. Immune system

The immune system of the human body is a complex network of molecules, cells and organs that interact and communicate together to respond to the invasion of pathogens and maintain the body's homoeostasis (Thompson, 2015). The immune system consists of innate immunity, which is a stereotyped rapid response to a stimulus, and adaptive immunity, which is a slower but highly specific response (Iwasaki & Medzhitov, 2015). The innate immune response operates in conjunction with the adaptive through activation of signalling pathways (O'neill et al., 2013). Figure 1 gives an overview of the interactions between the innate and adaptive responses of the immune system.

2.1. Innate immune system

The innate immune system is the first line of defence in the human body and is composed of three stages (Orlowsky & Kraus, 2015). The first stage is the chemical and physical barriers while the second stage depends on cell-intrinsic mechanisms and digestive enzymes which destroy viruses, bacteria and other pathogenic invaders (Medzhitov & Janeway Jr, 2000; Mogensen, 2009; Iwasaki & Pillai, 2014; Iwasaki & Medzhitov, 2015). The third stage of defence relies on the recognition of preserved pathogenic features (pathogen-associated immune-stimulants) by the complementary system and phagocytosis by immune cells such as natural killer cells, neutrophils and macrophages (McCarthy et al., 2014). Pathogenic immune stimulants are referred to as Pathogen-Associated Molecular Patterns (PAMPs) and they include pathogen cell wall polysaccharides such as chitin and mannans from fungi, lipoolysaccharides (LPS) from Gram-negative bacteria and peptidoglycan from Gram-positive bacteria (Volman et al., 2008; Kawai & Akira, 2010; Wiersinga et al., 2014).

PAMPs have been well studied, especially LPS (Okuda et al., 2016). This has the ability to initiate the host defence through recognition of its bioactive component, lipid A, via co-receptor

MD-2 and Toll-Like Receptor 4 (TLR4) (Saitoh et al., 2004; Ohto et al., 2012; Kang et al., 2016). The structure of lipid A is composed of two glucosamine units with a β(1→6) linkage attached to six fatty acyl chains, 1 and 4 phosphate groups (Slocum et al., 2014; Trouw et al., 2017). It has been reported that optimal immune activation of lipid A is derived from the acyl chains attached directly to the di-glucosamine (Raetz et al., 2009).

The complement system is part of the innate immune system (Galluzzi et al., 2017) and is responsible for enhancing the ability of phagocytic cells to clear damaged cells and microbes from the system (Orsini et al., 2014). Three pathways have been identified for complement activation, which are the classical, alternative and lectin pathway (Takahashi et al., 2008; Merle et al., 2015). IgG or IgM antigen/antibody complexes are responsible for initiating the classical pathway through binding to the first protein of the cascade (C1q) which in turn activates the C1r, leading to formation of the membrane attack complex which eventually penetrates bacterial membranes creating pores which lead to bacterial lysis (Peerschke et al., 2016).

The second pathway of the complement system is known as the alternative pathway or 'properdin pathway', which is a failure to regulate low-level continuous formation of C3 convertase (Miwa et al., 2013). Eventually, if a product of C3 convertase called C3b binds to a bacterial cell surface, this creates an amplification loop for other pathways (Galluzzi et al., 2017; Trouw et al., 2017).

The lectin pathway involves mannose-binding lectin (MBL). The initiating molecules for this pathway (MBL and ficolin) are multimeric lectin complexes (Amiri, 2015). These molecules bind to specific carbohydrates in the host to activate the pathway through enzymatic activity of mannan-binding lectin-associated serine protease (MASP). The structural similarities between C1 and MBL suggest that complement activation by C1 and MBL involves similar pathways (Kozarcanin et al., 2016).

All three pathways have the ability to activate the key components C 1-3, referred to as C3. This activation is critical for the complementary reaction as it triggers the inflammatory response, which in turn activates components C 5-9 (Ali et al., 2012).

Activation of C 5-9 triggers a cascade of events that leads to activation and recruitment of other innate immune cells (Garred et al., 2016). The PAMPs from the invaders bind to Pattern Recognition Receptors (PRRs) which are displayed on host immune cells (Takeuchi & Akira, 2010; Kagan & Barton, 2015). PRRs include the Toll-Like Receptors (TLRs) which are found on the surface of phagocytes (dendritic cells, neutrophils and macrophages) (De Nardo, 2015). For example, Toll-Like Receptor-4 (TLR4) activates the innate immune response through recognition of LPS from the cell wall of Gram-negative bacteria (He et al., 2014).

Post-activation, immune cells such as neutrophils, dendritic cells and macrophages secrete cytokines to communicate with other cells in the immune system and stimulate the immune response (Guilliams et al., 2014). On the other hand, activation of innate immune cells produces digestive enzymes and reactive oxygen radicals that destroy pathogens (Takahashi et al., 2008). Furthermore, dendritic cells play an important role in transferring ingested pathogens to the lymph nodes to activate T lymphocytes, thereby initiating a specific immune response that is part of the adaptive immune system (Kim et al., 2006; Ait-Oufella et al., 2014).

2.2. Adaptive immune system

Adaptive immunity protects the human body from certain death by infection (Wong et al., 2014). Once the innate response is initiated, it calls the adaptive immune system into play; then both work together to eliminate pathogens (Zhu et al., 2015). Unlike the innate immune response, the adaptive immune response is slow but highly specific against pathogens, and its protection is long-lasting (Cooper & Alder, 2006). It is pointless to mount the adaptive immune response against harmless foreign molecules, otherwise the adaptive immune response might

158 be deleterious (Witztum & Lichtman, 2014). This is normally avoided because the adaptive
159 immune response is triggered by the innate immune system only when the latter recognises
160 molecules of the attacking pathogens such as PAMPs (Bonneaud et al., 2003; Lu et al., 2016).

161 Dendritic cells, also known as pathogen-presenting cells, have surfaces packed with PRRs,
162 which bind to the PAMPs of foreign pathogens and initiate phagocytosis (Visintin et al., 2001;
163 Gringhuis et al., 2014). The dendritic cells, with the ingested pathogens, then move to a
164 peripheral lymphoid organ or to a nearby lymph node where the dendritic cells present the
165 antigens of the ingested pathogens to T lymphocytes (Cravens & Lipsky, 2002; Gringhuis et
166 al., 2014). The cell surface of T cells is covered with various receptors that recognise
167 extraneous antigens such as foreign polysaccharides or large proteins (Caramalho et al., 2003;
168 Levine, 2015). To complete the activation of T cells, a co-stimulatory signal is sent from the
169 dendritic cells, resulting in proliferation of T cells with the same receptor, thereby inducing
170 antigen-specific adaptive immune responses (Chen & Flies, 2013). To eliminate the pathogen
171 at the infection site, T cells mature and differentiate into different types of effector T cells
172 including cytotoxic, helper and regulatory T cells (Mucida et al., 2013; Nishikawa &
173 Sakaguchi, 2014). Cytotoxic T cells have the ability to detect substantial number of different
174 antigens with high specificity and release lytic proteins thus eliminating pathogens that
175 proliferate inside the host cell (Jones et al., 2017).

176 Helper T cells can release cytokines that guide dendritic cells to stay in their active form and
177 can stimulate antibody production from B cells that kill pathogens (Rissoan et al., 1999; Ise et
178 al., 2014). Helper T cells can also express co-stimulatory proteins on their surface and release
179 cytokines to activate more cytotoxic T cells and macrophages (Croft, 2003; Maude et al., 2014).
180 The regulation and control of activated immune cells is mediated by regulatory T cells, which
181 can inhibit the activity of cytotoxic T cells, helper T cells and dendritic cells to avoid
182 autoimmunity (Sakaguchi et al., 2008; Ito et al., 2016). Activated B cells secrete serum proteins

and synthesize antibodies that bind directly to pathogens to inactivate them. They also recruit innate immune cells such as macrophages to eliminate invaders (Clark & Ledbetter, 1994; Amable et al., 2014).

2.3. Monocytes

Monocytes are white cells circulating in the blood (Guilliams et al., 2014). They can express CD11b and Toll-like receptor-4 (TLR4) associated with CD14, which are triggered by LPS from the cell wall of Gram-negative bacteria (Taylor et al., 2005; Frantz et al., 2013). Monocytes originate from haematopoietic stem cells in the bone marrow (Lee et al., 2015) and activation of these stem cells results in the differentiation of common myeloid progenitors (CMPs) which differentiate further into macrophage and granulocyte progenitors (Ogawa, 1993; Ginhoux & Jung, 2014). Prior to the transformation of haematopoietic stem cells into circulating monocytes, they undertake a series of embryonic divisions (Chow et al., 2011; Lim et al., 2013). Monocytes circulate in the blood and have the potential to differentiate into dendritic cells or macrophages (Geissmann et al., 2010; Heidt et al., 2014). Differentiation to macrophages requires the activation of runt-related transcription factor that encodes the ETS family transcription factor PU.1, which needs to be constantly expressed at high levels to induce monocyte differentiation to macrophages (Lawrence & Natoli, 2011; Schneider et al., 2014).

2.4. Macrophages

Monocytes circulate in the blood for up to two days followed by migration into tissues and differentiation into macrophages (van Furth & Cohn, 1968; Geissmann et al., 2010). Macrophages and neutrophils have the ability to take up pathogens through phagocytosis, a process which engulfs large particles (> 0.5 μm) into cells through an actin-dependent

mechanism (Silva, 2010; Linehan et al., 2014). Activation of macrophages and subsequent phagocytosis occurs through PAMP-mediated recognition of Gram-negative and Gram-positive bacteria by PRRs (Plüddemann et al., 2011; Martinez & Gordon, 2014). Macrophages have a range of PRRs including TLR, which when activated results in pro-inflammatory cytokine production including IL-23, IL-12, IL-6 and TNFα (Mosser & Edwards, 2008; O'neill & Pearce, 2016). Activated macrophages also express inducible nitric oxide synthase (iNOS), which is responsible for generating nitric oxide (NO), a key mediator for killing bacteria within macrophages (Murray et al., 2014; Martins et al., 2017).

2.5. Initiate immune responses

PAMPs are responsible for initiating the innate immune response through PRRs, of which the TLR family has been extensively investigated in recent years (Medzhitov, 2001; Akira & Takeda, 2004; Pradere et al., 2014). On recognition of PAMPs, PRRs at the cell surface triger intracellular pathways that lead to the transcription of chemokines and cytokines involved in antimicrobial and proinflamatory responses (Akira & Takeda, 2004; Gazendam et al., 2016).

2.6. Toll-like receptor family (TLRs)

The most investigated class of PRRs is the TLR family. The name is derived from their homology to the Toll protein in *Drosophila melanogaster* (Medzhitov et al., 1997; De Nardo, 2015; Murofushi et al., 2015). The structural hallmarks of all known TLRs are an extracellular cysteine-rich domain, leucine-rich motifs (LRR) and a cytoplasmic signalling Toll/IL-1 receptor (TIR) analogy domain in the intracellular region (Gay & Keith, 1991; Pietretti et al., 2014; Ren et al., 2014). The intracellular signal transduction is due to receptor oligomerisation that is induced by ligand binding to TLRs (Futosi et al., 2013). To date, 10 TLRs have been identified in mammals, and each recognize distinct PAMPs derived from bacteria, viruses, fungi and protozoa (Akira & Takeda, 2004; Bonham et al., 2014).The TLRs include TLR1,

TLR2, TLR4 and TLR6 that recognize lipoproteins such as triacyl lipopeptides and LPS, while TLR3, TLR7, TLR8 and TLR9 recognize nucleic acids such as dsRNA or ssRNA (Curtale et al., 2013; Vacchelli et al., 2013; Gay et al., 2014).

2.7. Lipopolysaccharides (LPS)

LPS are a major component of the cell wall of Gram-negative bacteria (Guha & Mackman, 2001), consisting of three parts; a polysaccharide side chain also known as O-antigen or O-chain, a non-repeating core polysaccharide, and lipid A, which is hydrophobic (Speciale et al., 2015). The polysaccharide side chain and non-repeating core polysaccharide are projections from the surface, while the hydrophobic domain is embedded in the outer membrane. The lipid A domain is a source of toxicity, while the O-chains are easily detected by the host antibodies and, to avoid detection, are often modified by bacteria (Lerouge & Vanderleyden, 2002; Miller et al., 2005; Eckert et al., 2013; Wu et al., 2013). Lipopolysaccharide structure is illustrated in Figure 2. Low levels of LPS are sufficient to induce a substantial inflammatory response of the innate immune system (Schwarz et al., 2014). LPS binds to the LPS Binding Protein (LBP) in serum, before being transferred to CD14 and then to MD2, which is associated with TLR4 (Ryu et al., 2017). The receptor complex then promotes secretion of nitric oxide (NO) and pro-inflammatory cytokines such as TNFα and IL-8 in monocytes and macrophages (Johnson et al., 2002; Termeer et al., 2002; Miller et al., 2005; Massey et al., 2015; Lee et al., 2016).

2.8. Cytokines

Cytokines are small, soluble proteins that affect the function or growth of cells. Cytokines can act in a paracrine way (affect nearby cells) or an autocrine way (affect the same cell). However, some cytokines such as IL-6, IL-8 and TNFα can have systemic effects. Cytokines act on immune cells and mediate inflammatory responses (Vilček & Feldmann, 2004; Le Maitre, 2014).

2.9. Tumour necrosis factor alpha (TNFα)

TNFα is a pro-inflammatory cytokine with various biological effects (Bekkering et al., 2014). TNFα is involved in apoptosis, differentiation and proliferation (Du et al., 2014; Sullivan et al., 2014) and levels are elevated in inflammatory diseases such as rheumatoid arthritis (Motley et al., 2004; Garraway et al., 2014). Two receptors are known to mediate the effects of TNFα, TNFR1 and TNFR2. Local TNFα production is critical for elimination of local infections (Motley et al., 2004; Olmos & Lladó, 2014). Systemic TNFα release also plays a vital role in septic shock (Kanashiro et al., 2017). TNFα is released in macrophages and monocytes in response to foreign stimuli such as LPS from Gram-negative bacteria. The secretion of TNFα from T-cells is initiated by activation of the T-cell receptor (Manzo et al., 2017). In addition, natural killer cells and B cells can produce TNFα (Eissner et al., 2000; Yu et al., 2009). The effect of TNFα on endothelial cells includes the upregulation of leukocyte adhesion molecules that contribute to leukocyte recruitment (Huang et al., 2015).

2.10. Nitric oxide (NO)

Nitric oxide (NO) is a shor t-lived, gaseous, small molecule composed of one atom of oxygen and one atom of nitrogen, thus making it a free radical due to unpaired electrons (Pacher et al., 2007). In the human body, NO is defined as a product of macrophage activation by pro-inflammatory cytokines, microbial endotoxins such as LPS, or both (Rath et al., 2014). NO is a product of L-arginine degradation, the reaction being catalysed by an enzyme called inducible nitric oxide synthase (iNOS) (Bogdan, 2001; Palygin et al., 2015). This reaction requires several cofactors including calcium/calmodulin, flavin mononucleotide (FMN), nicotinamide adenine dinucleotide phosphate (NADPH), flavin adenine dinucleotide (FAD), tetrahydrobiopterin (BH4), oxygen and haem (Baek et al., 1993; Marletta, 1994). There are three known isoforms of NOS; their names come from where they were first found. Inducible

NOS (iNOS) was found in macrophages, endothelial NOS (eNOS) found in endothelial cells and the neuronal NOS (nNOS) found in the brain. These isoforms are also known as NOS-2, NOS-3 and NOS-1 respectively (Alderton et al., 2001; Bogdan, 2015).

2.10.1. NO role in macrophages

NO production in macrophages depends on their activation in response to cytokine or bacterial endotoxin stimuli (Sadek et al., 2017). Macrophages act as patrolling cells and produce low levels of NO in quiescent conditions (Prolo et al., 2015). However, once activated by stimuli, macrophages produce excessive amounts of NO, releasing NO_2- and NO_3-, which are important in pathogen scavengers (Marletta et al., 1988; Hibbs, 2002). Although NO production is critical for macrophage phagocytosis, an excessive amount of NO has been associated with high levels of necrosis and apoptosis (He et al., 2016; Jakubowska et al., 2016). It has been reported that high levels of NO induce autoimmune reactions such as asthma and arthritis (Scichilone et al., 2013), so it is crucial to dampen NO production in such conditions. Evidence suggests the modulation of immune function can be achieved by food (Zeng et al., 2016).

2.11. Immunomodulating properties of food

The functionality of the immune system is crucial for protecting the body from the attacks of pathogens or from cancer cell proliferation (Mittal et al., 2014). Thus, it plays a vital role in health homoeostasis (Nairz et al., 2013). However, many factors disturb immune functions such as an unhealthy lifestyle, malnutrition, physical stress, disease and ageing (Nahrendorf & Swirski, 2015). Evidence suggests that the ingestion of foods with immuneomodulatory effects prevents declining immune function or reduces the risk of infection (Kaminogawa & Nanno, 2004; Goldsmith & Sartor, 2014). There are many studies suggesting that foods can improve depressed immune function by moderating the severity of infectious diseases and reducing infection rates (El-Gamal et al., 2011; Rajilić-Stojanović et al., 2015). Thus, foods with the

303 ability to improve immune responses, particularly in patients with impaired immunity such as
304 cancer (Braga et al., 1996; Bradbury et al., 2014; Schnekenburger et al., 2014), are both
305 clinically and commercially valuable.

306 **3. Arabinoxylans**

307 Arabinoxylan is a non-starch polysaccharide (Figure 3) with a backbone of β-(1-4)-linked d-
308 xylopyranosyl residues to which α-l-arabinofuranose units are linked as side chains in the
309 second and/or third carbon-positions (Courtin et al., 2000; Roubroeks et al., 2000; Zhou et al.,
310 2010; Qiu et al., 2017).

311 Arabinoxylan structure is characterised by substitution of the xylopyranose- linked xylan
312 backbone. L-Arabinofuranose is the main sugar substitute for xylopyranose residues at O-2
313 and/or O-3 via α-1, 2 and α- 1, 3 glycosidic linkages. This leads to three different forms namely,
314 un-substituted xylopyranose, mono-substituted xylopyranose at O-2 or O-3 and di-substituted
315 xylopyranose at O-2 and O-3 (Izydorczyk & Biliaderis, 1995; Saulnier et al., 2007; Broekaert
316 et al., 2011; Qiu et al., 2017). However, arabinofuranose substitutions can form short
317 oligosaccharide side chains that comprise of two or more arabinofuranose residues (Figure 4)
318 (Saulnier et al., 2007).

319 There are many techniques available for arabinoxylan extraction and different extraction
320 methods give different yields and degrees of branching, molecular weight distribution and
321 tertiary conformation (Lu et al., 2005), i.e. hot water extraction (Izydorczyk et al., 1998; Cyran
322 et al., 2003; Iqbal et al., 2011; Yu et al., 2017) and ultrasound-assisted enzymatic extraction
323 (Wang et al., 2014).

324 Arabinoxylans can be classified according to their solubility in water, as either water-
325 unextractable arabinoxylans (WUAX) or water-extractable arabinoxylans (WEAX) (Moers et
326 al., 2005). The structure of WUAX is different from that of WEAX as WUAX will not

327 solubilise in water, but will be solubilized in alkaline solutions (Gruppen et al., 1993). Table 1
328 shows the water-extractable and water-unextractable arabinoxylans in some cereals.

329 Reducing the molecular weight of the arabinoxylans not only increases their solubility in water
330 but also increases their biological health benefits (Li et al., 2013). Recently, pronounced effects
331 of low Mw arabinoxylans (66 kDa) have been observed to have a higher prebiotic stimulation
332 in an *in vitro* study compared to higher Mw arabinoxylans (Hughes et al., 2007). Modification
333 of the molecular characteristics of arabinoxylans such as Mw is important to achieve the
334 optimum prebiotic, anti-tumour activities and immune stimulation (Li et al., 2013).

335 It has been suggested that the activity of arabinoxylans is dependent on their sugar composition,
336 molecular weight and degree of branching (Zhou et al., 2010; Cao et al., 2011). The most
337 investigated type of arabinoxylans (MGN-3) has low molecular weight with a low arabinose-
338 to-xylose ratio (0.5) (Zhang et al., 2015) which is similar to the enzyme- extracted wheat bran
339 arabinoxylans (Zhou et al., 2010). Both polysaccharides could activate macrophages (Zhou et
340 al., 2010; Zhang et al., 2015). However, MGN-3 appeared to be more effective, which might
341 be due to differences in the sugar composition since MGN-3 has more glucose and galactose
342 side chains (Zhang et al., 2015). Figure 5. shows a simplified representation of the macrophage
343 TLR 4 receptor with arabinoxylans and LPS.

344 **3.1. Immunomodulatory potentials of arabinoxylans**

345 It has been reported that oral administration of arabinoxylans extracted from wheat bran using
346 xylanases and alkali extraction has an immune-modulatory effect on both the innate and
347 adaptive immune systems (Zhou et al., 2010; Cao et al., 2011). Alkali extracted arabinoxylans
348 from wheat bran showed inhibitory effects on tumour growth and IL-2 production at 100-400
349 mg/kg on S 180 tumour bearing mice. The most significant results were at the highest

concentration (400 mg/kg). Moreover, there was an increase in leukocyte count, and stem cell proliferation was enhanced after oral administration (Cao et al., 2011).

Another study conducted by Zhou et al. (2010) indicated that (200 mg/kg) oral administration of enzyme-extracted wheat bran arabinoxylans exhibited immunostimulatory effects on both innate and adaptive immunity. The enzyme-extracted arabinoxylans stimulated phagocytosis by macrophages and delayed hypersensitivity more than alkaline-extracted arabinoxylans (Zhou et al., 2010).

Recently, Li et al. (2015) investigated the effect of enzyme-extracted arabinoxylans (AXE) from wheat endosperm pentosan on U937 and Caco-2 cell lines. They reported that AXE generated higher nitric oxide (NO) levels than (WEAX) and the increase in NO production was dose-dependent. AXE was reported to be more effective than WEAX in stimulating IL-8 production (Li et al., 2015).

Previous studies suggested that arabinoxylans from various sources have immunomodulatory potential. It is clear that there are several factors affecting the immunomodulatory potential of arabinoxylans including the method of extraction, enzyme/chemical treatments and botanical source. Table 2 shows the structural activity of arabinoxylans from rice bran and wheat on different cells.

3.2. Potential arabinoxylan receptors

Although receptors for arabinoxylans have not been identified, some potential receptors have been proposed. AXs maybe acting like PAMPs since AXs from cornhusk and rice bran have shown similarities in terms of molecular weight and structure to LPS from Gram-negative bacteria (Ghoneum & Brown, 1999; Ogawa et al., 2005; Mendis et al., 2017). For example, LPS has outer core hexoses such as glucose and galactose, which are found in AXs. Another similarity between the structure of LPS and AXs includes C-3 branched polysaccharides

(Rietschel et al., 1994; Heinrichs et al., 1998). Moreover, AXE from wheat endosperm pentosan had low Mw (1-25 kDa) (Li et al., 2015) which is within the molecular weight range (13-20 kDa) of LPS (Mangoni et al., 2008). Therefore, arabinoxylans may activate phagocytes by attaching to Toll-like receptors expressed on their cell surface (Zhang et al., 2015). Since LPS specifically binds to TLR4, it suggests that TLR4 may also be a potential receptor for arabinoxylans (Mendis et al., 2016). If true, arabinoxylans may compete with LPS for the TLR4 receptor during infection, thus mediating the LPS-induced immune response.

Other receptors besides TLRs may also act as receptors for arabinoxylans. These include the Dectin-1 receptor, which has been reported to be a β glucan receptor (Karumuthil-Melethil et al., 2014; Kanjan et al., 2017). However, Sahasrabudhe et al. (2016) have reported recently that arabinoxylan from wheat has the ability to stimulate Dectin-1 receptors and it enhanced Interleukin 23 (IL-23), and Interleukin 4 (IL-4) expression in Dectin-1 stimulated dendritic cells (Sahasrabudhe et al., 2016).

3.3. Structure-activity relationship

The most investigated type of arabinoxylans (MGN-3) has a low molecular weight with a low arabinose- to-xylose ratio (0.5) (Zhang et al., 2015) which is similar to the enzyme- extracted wheat bran arabinoxylans (Zhou et al., 2010). Both polysaccharides appear to activate macrophages but MGN-3 appeared to be more effective, which might be due to the higher sugar composition (Zhang et al., 2015). Figure 5. shows a simplified representation of the macrophage TLR 4 receptor with arabinoxylans and LPS.

4. Conclusions

Cereals are by far the most important source of food all over the world. Arabinoxylans are the major non-starch polysaccharides in most of the cereals. Also, it has been reported that

arabinoxylans have immune-modulatory activities. The immunomodulatory potentials of arabinoxylans have been linked to their sugar composition, molecular weight and degree of branching. Furthermore, there are structural similarities between arabinoxylans and LPS in terms of molecular weight and structure, suggesting that arabinoxylans can modulate the immune response through activation the LPS receptor TLR 4. Future work should focus on understanding more of the arabinoxylan mechanism of action, which might help in modulating the immune response more efficiently.

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993 Table 1. Water extractable and water-unextractable AXs in some cereals (dry weight basis)

994 weight basis

WEAX and WUAX in some cereal grains and cereal by-products (dry weight basis)					
Cereal	Tissues	Total AXs %	WEAX %	WUAX %	References
Rice	Bran	4.84-5.11	0.35-0.77	4.34-4.49	(Hashimoto, Shogren, Bolte, et al., 1987)
	Bran	8.5	0.2	8.3	(Choct, 1997)
	Hulls	8.36-9.24	0.11	8.25-9.13	(Hashimoto, Shogren, Bolte, et al., 1987)
	Cooked	0.5	NA	NA	(Dodevska et al., 2013)
	Germinated whole grain	2.97-6.84	NA	NA	(Kim et al., 2015)
	Whole grain	2.64	0.06	2.58	(Hashimoto, Shogren, Bolte, et al., 1987)
Wheat	Bran	25	1	24	(Hollmann & Lindhauer, 2005)
	De-starched bran	29.1	NA	NA	(Koegelenberg & Chimphango, 2017)
	Bran	26.2	NA	NA	(Koegelenberg & Chimphango, 2017)
	Bran	23	NA	NA	(Wang et al., 2015)
	Bran	19.38	0.88	18.5	(Hashimoto, Shogren, & Pomeranz, 1987)
	Endosperm	NA	8.23	NA	(Li et al., 2015)
	Endosperm	1.5-2.5	0.3-0.75	1.2-1.7	(Li et al., 2013)
	Endosperm	1.52-1.75	0.42-0.68	1.07-1.1	(Marcotuli et al., 2016)
	Flour	1.37-2.06	0.54-0.68	0.83-1.38	(Izydorczyk et al., 1991)
	White flour	5.1	2.1	2.96	(Pavlovich-Abril et al., 2016)
	Whole grain	5.77	0.59	5.18	(Hashimoto, Shogren, & Pomeranz, 1987)
	Whole grain	8.1	1.8	6.3	(Choct, 1997)

Rye	Whole grain	8-12.1	2.6-4.1	5.4-8	(Hansen et al., 2003)
	Bran	13	2.86-4.29	8.71-10.14	(Sárossy et al., 2013)
	Flour	3.2-3.64	2.2-2.65	0.99-1	(Cyran et al., 2003)
	Whole grain	8.9	3.4	5.5	(Choct, 1997)
Corn	Bran	29.86	0.28	29.58	(Hashimoto, Shogren, Bolte, et al., 1987)
	Bran	26.0	0.71	25.29	(Zhang et al., 2016)

995

996

997 **Table2. Structural properties of AXs**
998

Origin	Extraction method	Immunomodulatory activity	Mw (kDa)	Glu %	Gal %	Xyl %	Ara %	Ar/Xy	References
Wheat bran	alkaline	Tumour inhibition, Mφ activation	352	7.7	na	50.2	41.8	0.83	(Zhou et al., 2010)
Wheat bran	enzyme	Mφ activation	32.5	2.8	na	62.4	34.8	0.55	(Zhou et al., 2010)
Rice bran	enzyme	Mφ, DCs and NK activation	30-50	6	5-7	48-54	22-26	0.5	(Zhang et al., 2015)

999

Figure Legends

Figure 1. Simplified overview of the immune system; IL- interleukin, TNF α- tumour necrosis factor α, IF γ – interferon γ. Adapted from (Dranoff, 2004; Stevenson & Riley, 2004).

Figure 2. Lipopolysaccharide (LPS) structure

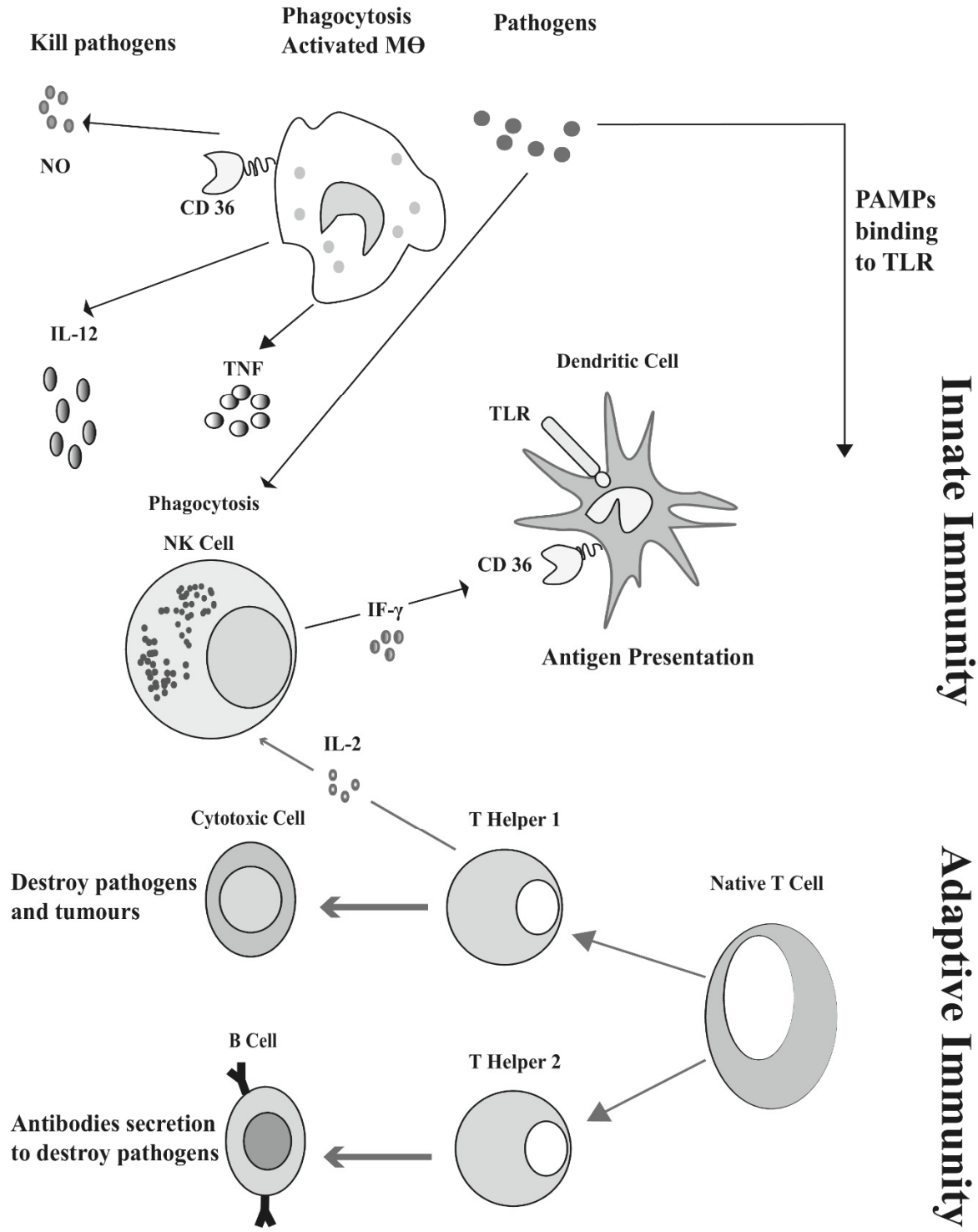
a. LPS lipid A, O-antigen and core oligosaccharide. b. TLR4-MD2-CD14 receptor complex (Miller et al., 2005).

Figure 3. Arabinoxylan structure (Garófalo et al., 2011).

Figure 4. Simplified schematic representation of arabinoxylans AXs

(a) Wheat flour and (b) Wheat bran. Substituents above and below the backbone represent C (O)-2 and C (O)-3 positions, respectively (Edwards et al., 2003; Zhou et al., 2010; Qiu et al., 2017).

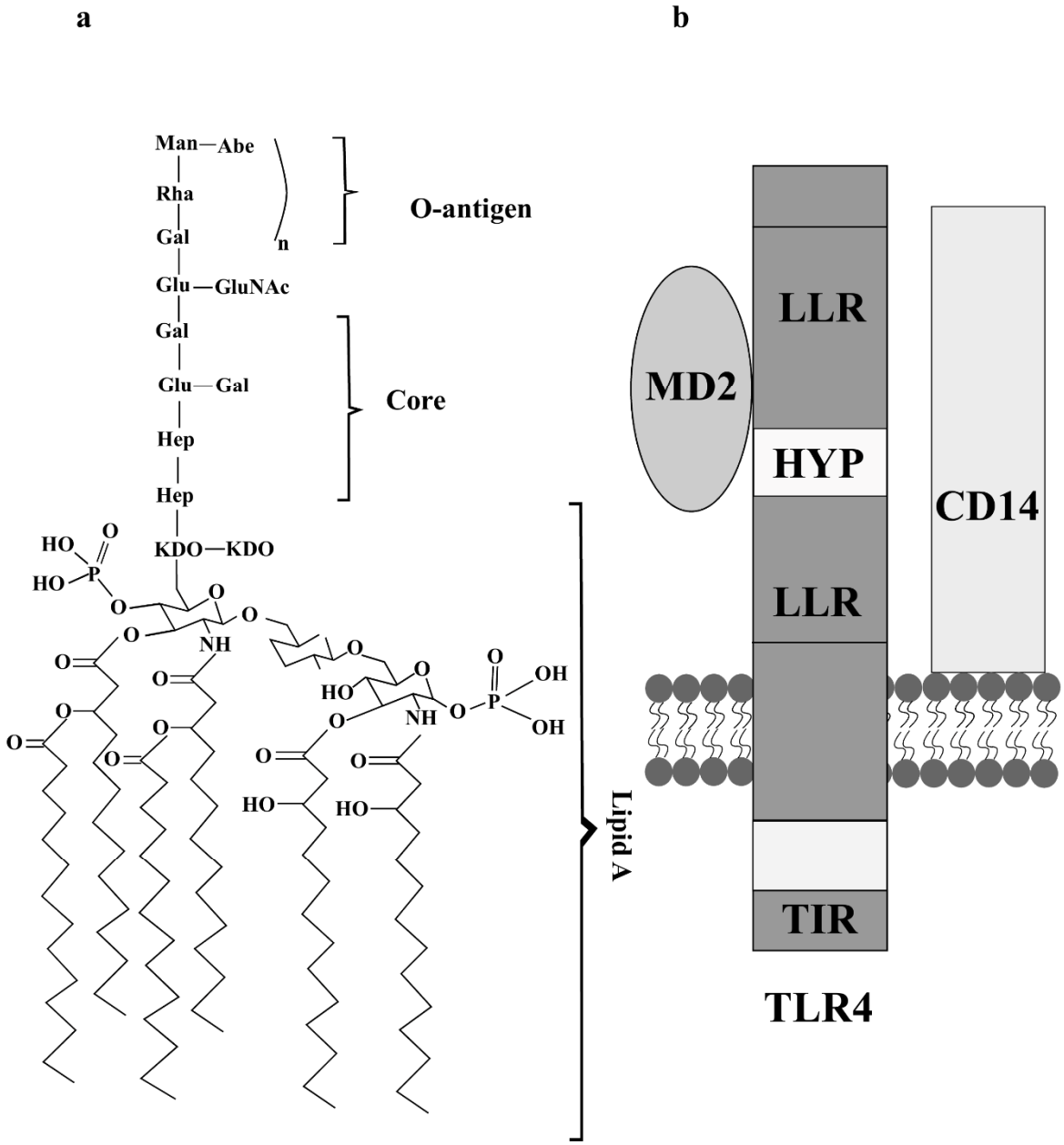
Figure 5. Simplified representation of the macrophage TLR 4 receptor with AXs and LPS



1020

1021 Figure 1. Simplified overview of the immune system; IL- interleukin, TNF α- tumour necrosis factor α, IF γ – interferon γ.

1022 Adapted from [33, 34]



1023

1024 Figure 2. Lipopolysaccharide (LPS) structure

1025 a. LPS lipid A, O-antigen and core oligosaccharide. b. TLR4-MD2-CD14 receptor complex [103].

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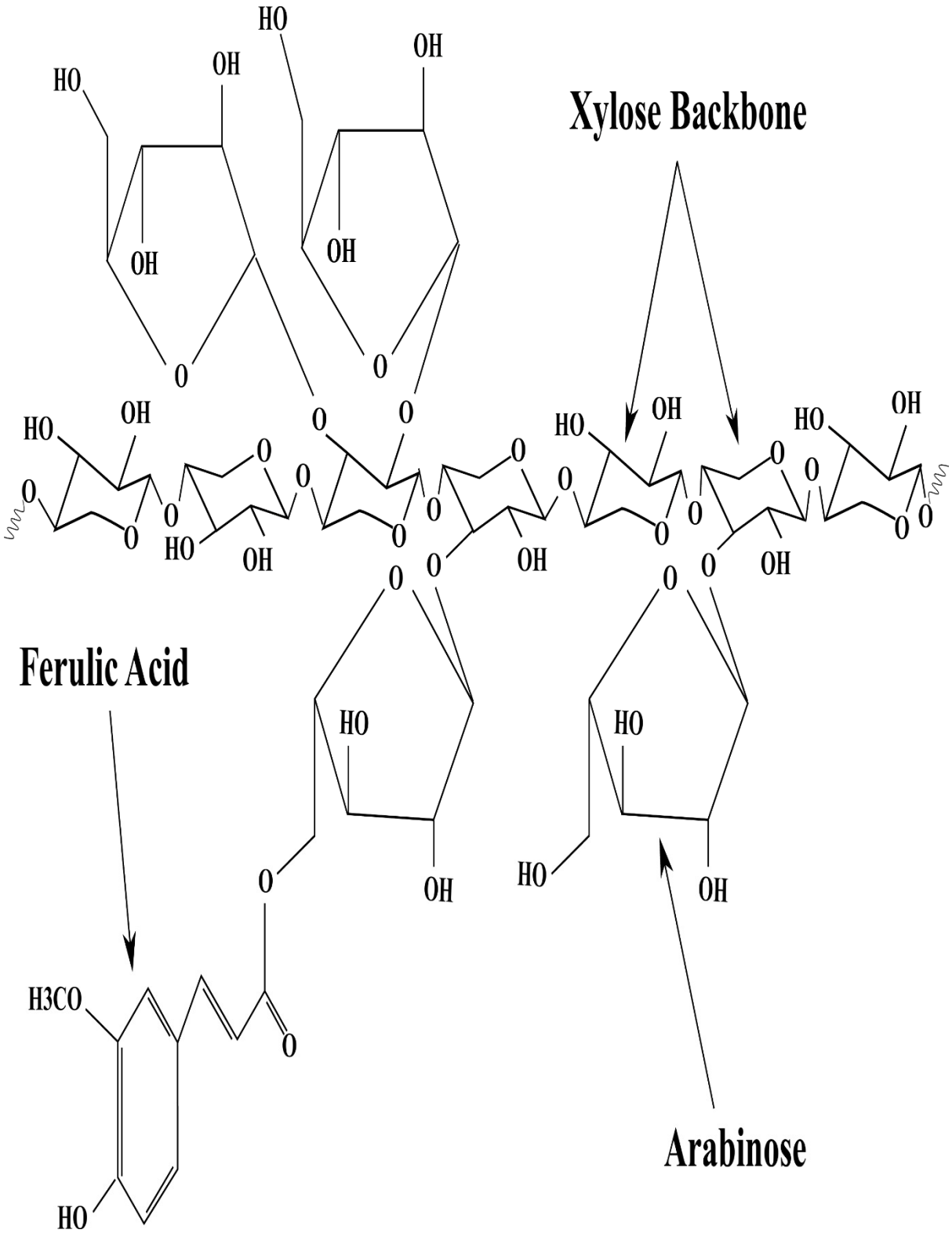


Figure 3. Arabinoxylan structure [140].

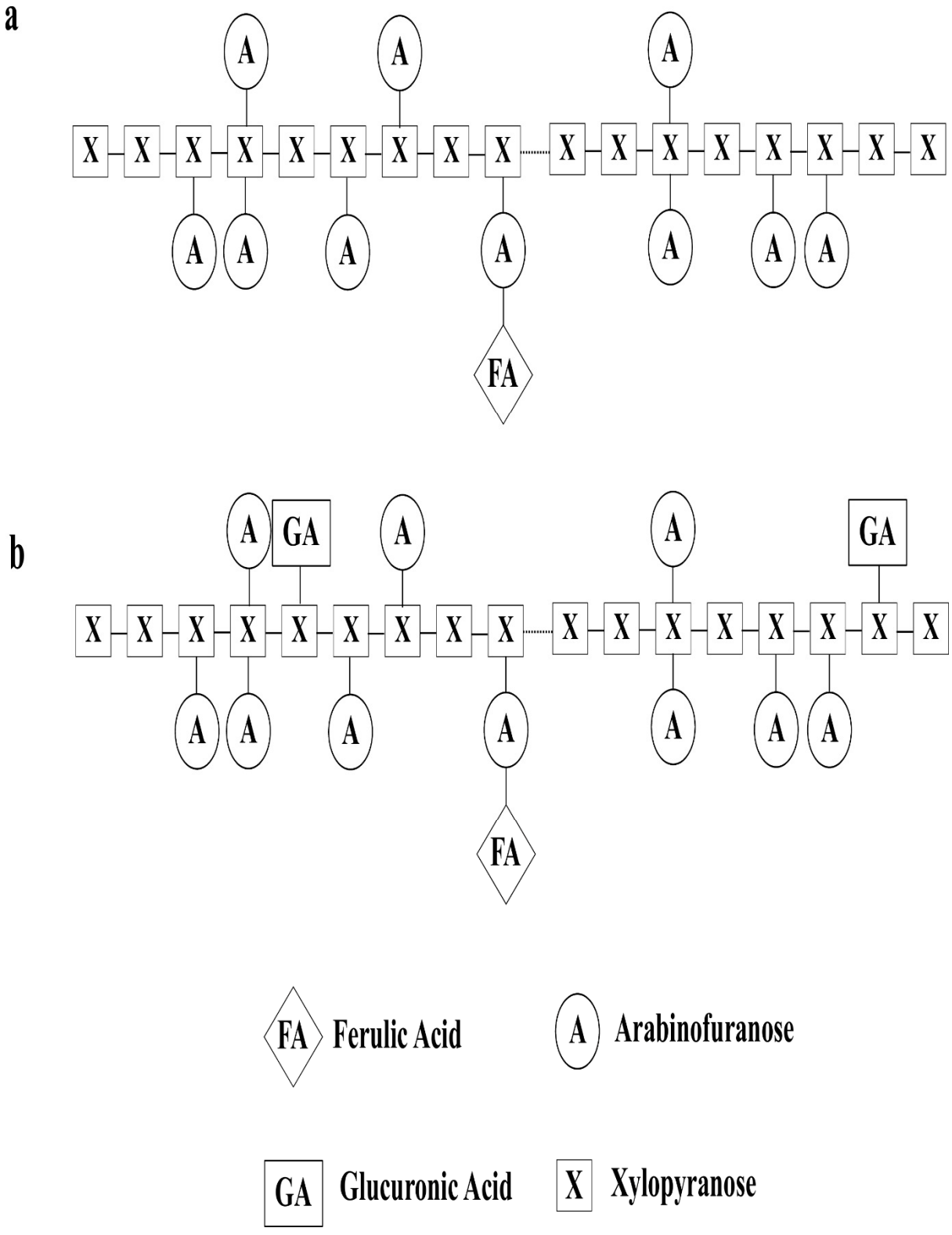
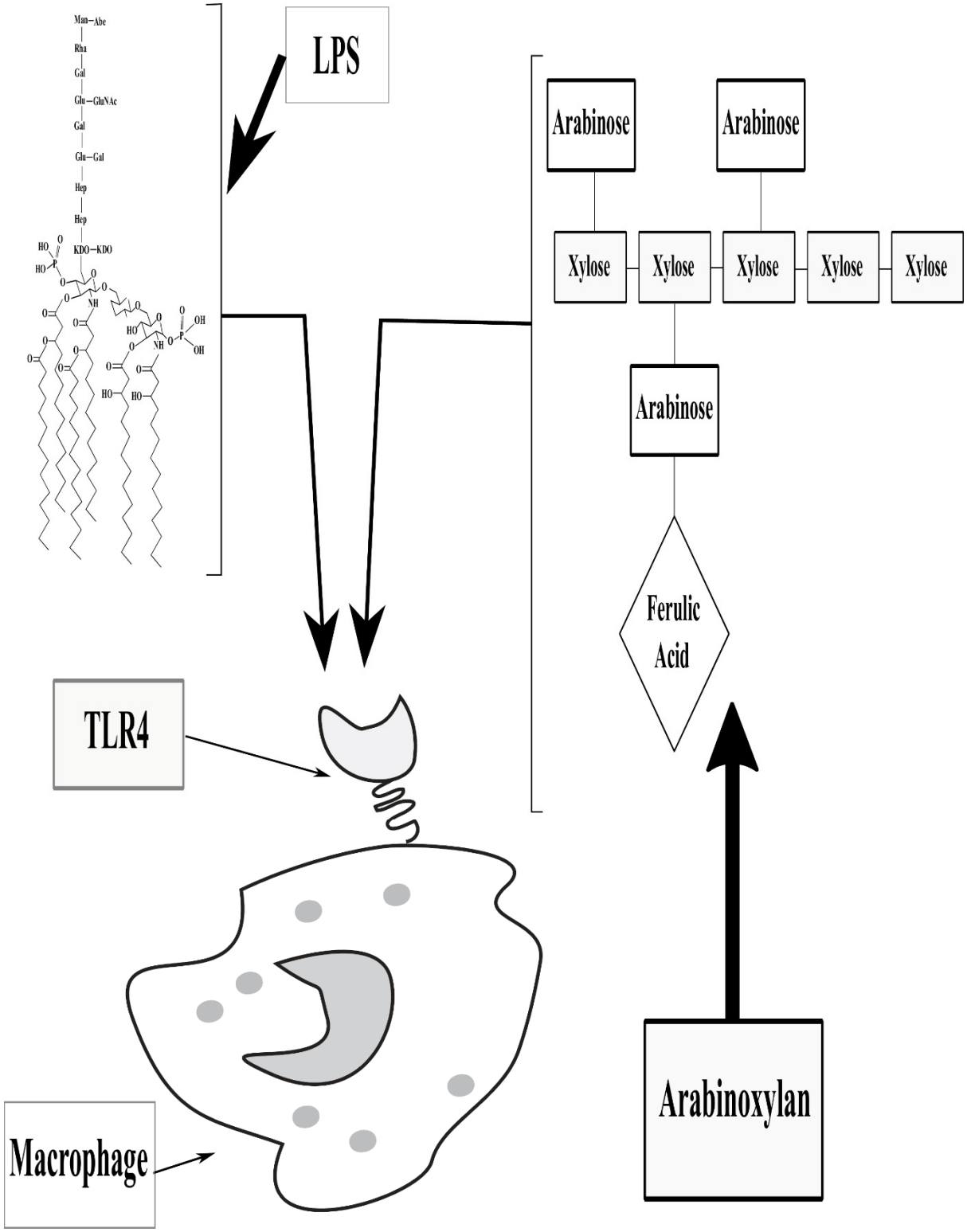


Figure 4. Simplified schematic representation of arabinoxylans AXs

(a) Wheat flour and (b) Wheat bran. Substituents above and below the backbone represent C (O)-2 and C (O)-3 positions, respectively [14, 139, 144].



1034

1035 Figure 5. Simplified representation of the monocyte TLR 4 receptor with AXs and LPS

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