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Item Type	Article
Authors	Fadel, Abdulmannan;Plunkett, Andrew;Li, Weili;Ashworth, Jason J.
Citation	Fadel, A., Plunkett, A., Li, W., & Ashworth, J. J. (2017). Modulation of Innate and Adaptive Immune Responses by Arabinoxylans. <i>Journal of Food Biochemistry</i> , 42(2), e12473. http://doi.org/10.1111/jfbc.12473
DOI	10.1111/jfbc.12473
Publisher	Wiley
Journal	Journal of Food Biochemistry
Download date	2026-05-11 09:33:08
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Link to Item	http://hdl.handle.net/10034/620940

1 **Modulation of Innate and Adaptive Immune Responses by Arabinoxylans**

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28 **Modulation of Innate and Adaptive Immune Responses by Arabinoxylans**

29 **Abstract**

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

39 **Practical applications**

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

50 infection by moderately activating the receptor and heightening natural (background) levels of
51 immunity.

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

54 **1. Introduction**

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

68 Performance of the immune system is vital for defending the body from pathogens and it plays
69 a crucial role in health homeostasis (Nairz et al., 2013). It has been suggested that ingestion
70 of foods with immune-modulatory effects is able to prevent deterioration of immune function
71 or reduce the risk of infection (Kaminogawa & Nanno, 2004; Goldsmith & Sartor, 2014).
72 Studies have suggested that diet can improve depressed immune function by moderating the
73 severity of infectious diseases and reducing infection rates (El-Gamal et al., 2011; Rajilić-

74 Stojanović et al., 2015). Cereals are staple foods and feed more than half of the world's
75 population; they are composed mainly of starch, protein, some minerals, and non-starch
76 polysaccharides that cannot be digested by human enzymes (Mohan et al., 2010). Arabinoxylan
77 is the main non-starch polysaccharide of many cereals (Zhou et al., 2010; Lovegrove et al.,
78 2017). It has been reported that arabinoxylan possesses immune-modulatory effects (Li et al.,
79 2015). Moreover, there is a structural similarity between arabinoxylans and the
80 lipopolysaccharides of Gram-negative bacteria (Park et al., 2009; Park et al., 2017). The aim
81 of this review is to give an overview of the immune system and how arabinoxylans might
82 modulate the immune response.

83

84 **2. Immune system**

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

93 **2.1. Innate immune system**

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

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

108 MD-2 and Toll-Like Receptor 4 (TLR4) (Saitoh et al., 2004; Ohto et al., 2012; Kang et al.,
109 2016). The structure of lipid A is composed of two glucosamine units with a $\beta(1\rightarrow6)$ linkage
110 attached to six fatty acyl chains, 1 and 4 phosphate groups (Slocum et al., 2014; Trouw et al.,
111 2017). It has been reported that optimal immune activation of lipid A is derived from the acyl
112 chains attached directly to the di-glucosamine (Raetz et al., 2009).

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

121 The second pathway of the complement system is known as the alternative pathway or
122 'properdin pathway', which is a failure to regulate low-level continuous formation of C3
123 convertase (Miwa et al., 2013). Eventually, if a product of C3 convertase called C3b binds to
124 a bacterial cell surface, this creates an amplification loop for other pathways (Galluzzi et al.,
125 2017; Trouw et al., 2017).

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

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

135 Activation of C 5-9 triggers a cascade of events that leads to activation and recruitment of other
136 innate immune cells (Garred et al., 2016). The PAMPs from the invaders bind to Pattern
137 Recognition Receptors (PRRs) which are displayed on host immune cells (Takeuchi & Akira,
138 2010; Kagan & Barton, 2015). PRRs include the Toll-Like Receptors (TLRs) which are found
139 on the surface of phagocytes (dendritic cells, neutrophils and macrophages) (De Nardo, 2015).
140 For example, Toll-Like Receptor-4 (TLR4) activates the innate immune response through
141 recognition of LPS from the cell wall of Gram-negative bacteria (He et al., 2014).

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

149 **2.2. Adaptive immune system**

150 Adaptive immunity protects the human body from certain death by infection (Wong et al.,
151 2014). Once the innate response is initiated, it calls the adaptive immune system into play; then
152 both work together to eliminate pathogens (Zhu et al., 2015). Unlike the innate immune
153 response, the adaptive immune response is slow but highly specific against pathogens, and its
154 protection is long-lasting (Cooper & Alder, 2006). It is pointless to mount the adaptive immune
155 response against harmless foreign molecules, otherwise the adaptive immune response might

156 be deleterious (Witztum & Lichtman, 2014). This is normally avoided because the adaptive
157 immune response is triggered by the innate immune system only when the latter recognises
158 molecules of the attacking pathogens such as PAMPs (Bonneaud et al., 2003; Lu et al., 2016).
159 Dendritic cells, also known as pathogen-presenting cells, have surfaces packed with PRRs,
160 which bind to the PAMPs of foreign pathogens and initiate phagocytosis (Visintin et al., 2001;
161 Gringhuis et al., 2014). The dendritic cells, with the ingested pathogens, then move to a
162 peripheral lymphoid organ or to a nearby lymph node where the dendritic cells present the
163 antigens of the ingested pathogens to T lymphocytes (Cravens & Lipsky, 2002; Gringhuis et
164 al., 2014). The cell surface of T cells is covered with various receptors that recognise
165 extraneous antigens such as foreign polysaccharides or large proteins (Caramalho et al., 2003;
166 Levine, 2015). To complete the activation of T cells, a co-stimulatory signal is sent from the
167 dendritic cells, resulting in proliferation of T cells with the same receptor, thereby inducing
168 antigen-specific adaptive immune responses (Chen & Flies, 2013). To eliminate the pathogen
169 at the infection site, T cells mature and differentiate into different types of effector T cells
170 including cytotoxic, helper and regulatory T cells (Mucida et al., 2013; Nishikawa &
171 Sakaguchi, 2014). Cytotoxic T cells have the ability to detect substantial number of different
172 antigens with high specificity and release lytic proteins thus eliminating pathogens that
173 proliferate inside the host cell (Jones et al., 2017).

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

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

184 **2.3. Monocytes**

185 Monocytes are white cells circulating in the blood (Guilliams et al., 2014). They can express
186 CD11b and Toll-like receptor-4 (TLR4) associated with CD14, which are triggered by LPS
187 from the cell wall of Gram-negative bacteria (Taylor et al., 2005; Frantz et al., 2013).
188 Monocytes originate from haematopoietic stem cells in the bone marrow (Lee et al., 2015) and
189 activation of these stem cells results in the differentiation of common myeloid progenitors
190 (CMPs) which differentiate further into macrophage and granulocyte progenitors (Ogawa,
191 1993; Ginhoux & Jung, 2014). Prior to the transformation of haematopoietic stem cells into
192 circulating monocytes, they undertake a series of embryonic divisions (Chow et al., 2011; Lim
193 et al., 2013). Monocytes circulate in the blood and have the potential to differentiate into
194 dendritic cells or macrophages (Geissmann et al., 2010; Heidt et al., 2014). Differentiation to
195 macrophages requires the activation of runt-related transcription factor that encodes the ETS
196 family transcription factor PU.1, which needs to be constantly expressed at high levels to
197 induce monocyte differentiation to macrophages (Lawrence & Natoli, 2011; Schneider et al.,
198 2014).

199

200 **2.4. Macrophages**

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

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

213 **2.5. Initiate immune responses**

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

219 **2.6. Toll-like receptor family (TLRs)**

220 The most investigated class of PRRs is the TLR family. The name is derived from their
221 homology to the Toll protein in *Drosophila melanogaster* (Medzhitov et al., 1997; De Nardo,
222 2015; Murofushi et al., 2015). The structural hallmarks of all known TLRs are an extracellular
223 cysteine-rich domain, leucine-rich motifs (LRR) and a cytoplasmic signalling Toll/IL-1
224 receptor (TIR) analogy domain in the intracellular region (Gay & Keith, 1991; Pietretti et al.,
225 2014; Ren et al., 2014). The intracellular signal transduction is due to receptor oligomerisation
226 that is induced by ligand binding to TLRs (Futosi et al., 2013). To date, 10 TLRs have been
227 identified in mammals, and each recognize distinct PAMPs derived from bacteria, viruses,
228 fungi and protozoa (Akira & Takeda, 2004; Bonham et al., 2014).The TLRs include TLR1,

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

232 **2.7. Lipopolysaccharides (LPS)**

233 LPS are a major component of the cell wall of Gram-negative bacteria (Guha & Mackman,
234 2001), consisting of three parts; a polysaccharide side chain also known as O-antigen or O-
235 chain, a non-repeating core polysaccharide, and lipid A, which is hydrophobic (Speciale et al.,
236 2015). The polysaccharide side chain and non-repeating core polysaccharide are projections
237 from the surface, while the hydrophobic domain is embedded in the outer membrane. The lipid
238 A domain is a source of toxicity, while the O-chains are easily detected by the host antibodies
239 and, to avoid detection, are often modified by bacteria (Lerouge & Vanderleyden, 2002; Miller
240 et al., 2005; Eckert et al., 2013; Wu et al., 2013). Lipopolysaccharide structure is illustrated in
241 Figure 2. Low levels of LPS are sufficient to induce a substantial inflammatory response of the
242 innate immune system (Schwarz et al., 2014). LPS binds to the LPS Binding Protein (LBP) in
243 serum, before being transferred to CD14 and then to MD2, which is associated with TLR4
244 (Ryu et al., 2017). The receptor complex then promotes secretion of nitric oxide (NO) and pro-
245 inflammatory cytokines such as TNF α and IL-8 in monocytes and macrophages (Johnson et
246 al., 2002; Termeer et al., 2002; Miller et al., 2005; Massey et al., 2015; Lee et al., 2016).

247 **2.8. Cytokines**

248 Cytokines are small, soluble proteins that affect the function or growth of cells. Cytokines can
249 act in a paracrine way (affect nearby cells) or an autocrine way (affect the same cell). However,
250 some cytokines such as IL-6, IL-8 and TNF α can have systemic effects. Cytokines act on
251 immune cells and mediate inflammatory responses (Vilček & Feldmann, 2004; Le Maitre,
252 2014).

253 2.9. Tumour necrosis factor alpha (TNF α)

254 TNF α is a pro-inflammatory cytokine with various biological effects (Bekkering et al., 2014).
255 TNF α is involved in apoptosis, differentiation and proliferation (Du et al., 2014; Sullivan et al.,
256 2014) and levels are elevated in inflammatory diseases such as rheumatoid arthritis (Motley et
257 al., 2004; Garraway et al., 2014). Two receptors are known to mediate the effects of TNF α ,
258 TNFR1 and TNFR2. Local TNF α production is critical for elimination of local infections
259 (Motley et al., 2004; Olmos & Lladó, 2014). Systemic TNF α release also plays a vital role in
260 septic shock (Kanashiro et al., 2017). TNF α is released in macrophages and monocytes in
261 response to foreign stimuli such as LPS from Gram-negative bacteria. The secretion of TNF α
262 from T-cells is initiated by activation of the T-cell receptor (Manzo et al., 2017). In addition,
263 natural killer cells and B cells can produce TNF α (Eissner et al., 2000; Yu et al., 2009). The
264 effect of TNF α on endothelial cells includes the upregulation of leukocyte adhesion molecules
265 that contribute to leukocyte recruitment (Huang et al., 2015).

266 2.10. Nitric oxide (NO)

267 Nitric oxide (NO) is a short-lived, gaseous, small molecule composed of one atom of oxygen
268 and one atom of nitrogen, thus making it a free radical due to unpaired electrons (Pacher et al.,
269 2007). In the human body, NO is defined as a product of macrophage activation by pro-
270 inflammatory cytokines, microbial endotoxins such as LPS, or both (Rath et al., 2014). NO is
271 a product of L-arginine degradation, the reaction being catalysed by an enzyme called inducible
272 nitric oxide synthase (iNOS) (Bogdan, 2001; Palygin et al., 2015). This reaction requires
273 several cofactors including calcium/calmodulin, flavin mononucleotide (FMN), nicotinamide
274 adenine dinucleotide phosphate (NADPH), flavin adenine dinucleotide (FAD),
275 tetrahydrobiopterin (BH₄), oxygen and haem (Baek et al., 1993; Marletta, 1994). There are
276 three known isoforms of NOS; their names come from where they were first found. Inducible

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

280 **2.10.1. NO role in macrophages**

281 NO production in macrophages depends on their activation in response to cytokine or bacterial
282 endotoxin stimuli (Sadek et al., 2017). Macrophages act as patrolling cells and produce low
283 levels of NO in quiescent conditions (Prolo et al., 2015). However, once activated by stimuli,
284 macrophages produce excessive amounts of NO, releasing NO₂⁻ and NO₃⁻, which are important
285 in pathogen scavengers (Marletta et al., 1988; Hibbs, 2002). Although NO production is critical
286 for macrophage phagocytosis, an excessive amount of NO has been associated with high levels
287 of necrosis and apoptosis (He et al., 2016; Jakubowska et al., 2016). It has been reported that
288 high levels of NO induce autoimmune reactions such as asthma and arthritis (Scichilone et al.,
289 2013), so it is crucial to dampen NO production in such conditions. Evidence suggests the
290 modulation of immune function can be achieved by food (Zeng et al., 2016).

291 **2.11. Immunomodulating properties of food**

292 The functionality of the immune system is crucial for protecting the body from the attacks of
293 pathogens or from cancer cell proliferation (Mittal et al., 2014). Thus, it plays a vital role in
294 health homeostasis (Nairz et al., 2013). However, many factors disturb immune functions
295 such as an unhealthy lifestyle, malnutrition, physical stress, disease and ageing (Nahrendorf &
296 Swirski, 2015). Evidence suggests that the ingestion of foods with immuneomodulatory effects
297 prevents declining immune function or reduces the risk of infection (Kaminogawa & Nanno,
298 2004; Goldsmith & Sartor, 2014). There are many studies suggesting that foods can improve
299 depressed immune function by moderating the severity of infectious diseases and reducing
300 infection rates (El-Gamal et al., 2011; Rajilić-Stojanović et al., 2015). Thus, foods with the

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

304 **3. Arabinoxylans**

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

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

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

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

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

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

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

342 **3.1. Immunomodulatory potentials of arabinoxylans**

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

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

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

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

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

365 **3.2. Potential arabinoxylan receptors**

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

372 (Rietschel et al., 1994; Heinrichs et al., 1998). Moreover, AXE from wheat endosperm
373 pentosan had low Mw (1-25 kDa) (Li et al., 2015) which is within the molecular weight range
374 (13-20 kDa) of LPS (Mangoni et al., 2008). Therefore, arabinoxylans may activate phagocytes
375 by attaching to Toll-like receptors expressed on their cell surface (Zhang et al., 2015). Since
376 LPS specifically binds to TLR4, it suggests that TLR4 may also be a potential receptor for
377 arabinoxylans (Mendis et al., 2016). If true, arabinoxylans may compete with LPS for the TLR4
378 receptor during infection, thus mediating the LPS-induced immune response.

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

385

386 **3.3. Structure-activity relationship**

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

393 **4. Conclusions**

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

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

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988 adaptive immune response to combination immunotherapy with anti-tumor antigen
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990

991 Table 1. Water extractable and water-unextractable AXs in some cereals (dry weight basis)
 992 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
De-starched bran		29.1	NA	NA	(Koegelenberg & Chiphango, 2017)
Bran		26.2	NA	NA	(Koegelenberg & Chiphango, 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)

Journal of Food Biochemistry

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)

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994

995
996**Table2. Structural properties of AXs**

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

997

998 **Figure Legends**

999 Figure 1. Simplified overview of the immune system; IL- interleukin, TNF α - tumour necrosis
1000 factor α , IF γ – interferon γ . Adapted from (Dranoff, 2004; Stevenson & Riley, 2004).

1001 Figure 2. Lipopolysaccharide (LPS) structure

1002 a. LPS lipid A, O-antigen and core oligosaccharide. b. TLR4-MD2-CD14 receptor
1003 complex (Miller et al., 2005).

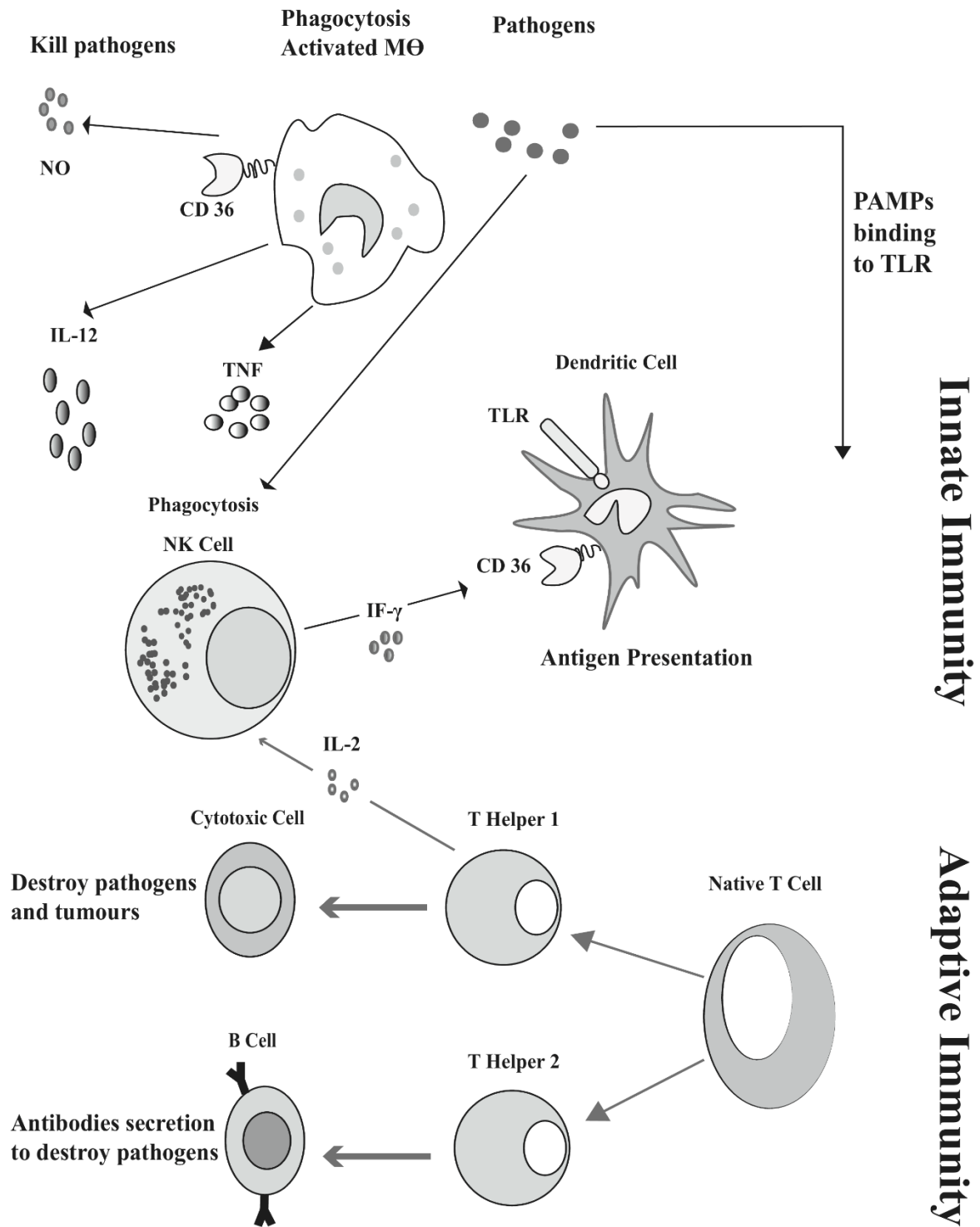
1004 Figure 3. Arabinoxylan structure (Garófalo et al., 2011).

1005 Figure 4. Simplified schematic representation of arabinoxylans AXs

1006 (a) Wheat flour and (b) Wheat bran. Substituents above and below the backbone represent
1007 C (O)-2 and C (O)-3 positions, respectively (Edwards et al., 2003; Zhou et al., 2010;
1008 Qiu et al., 2017).

1009 Figure 5. Simplified representation of the macrophage TLR 4 receptor with AXs and LPS

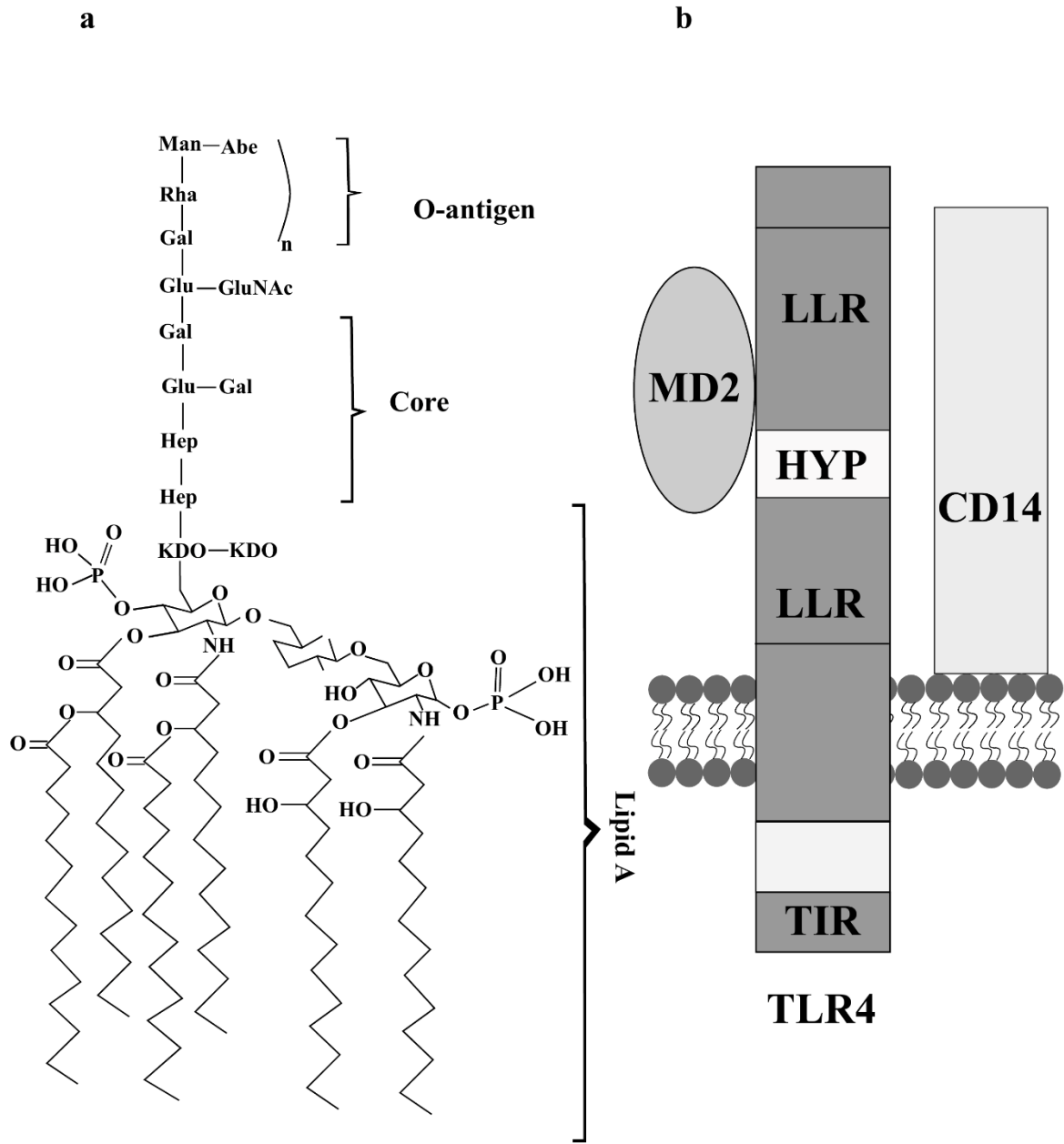
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1012 FIGURE 1. Simplified overview of the immune system; IL- interleukin, TNF α - tumour

1013 necrosis factor α , IF γ – interferon γ . Adapted from (Dranoff, 2004; Stevenson & Riley, 2004).



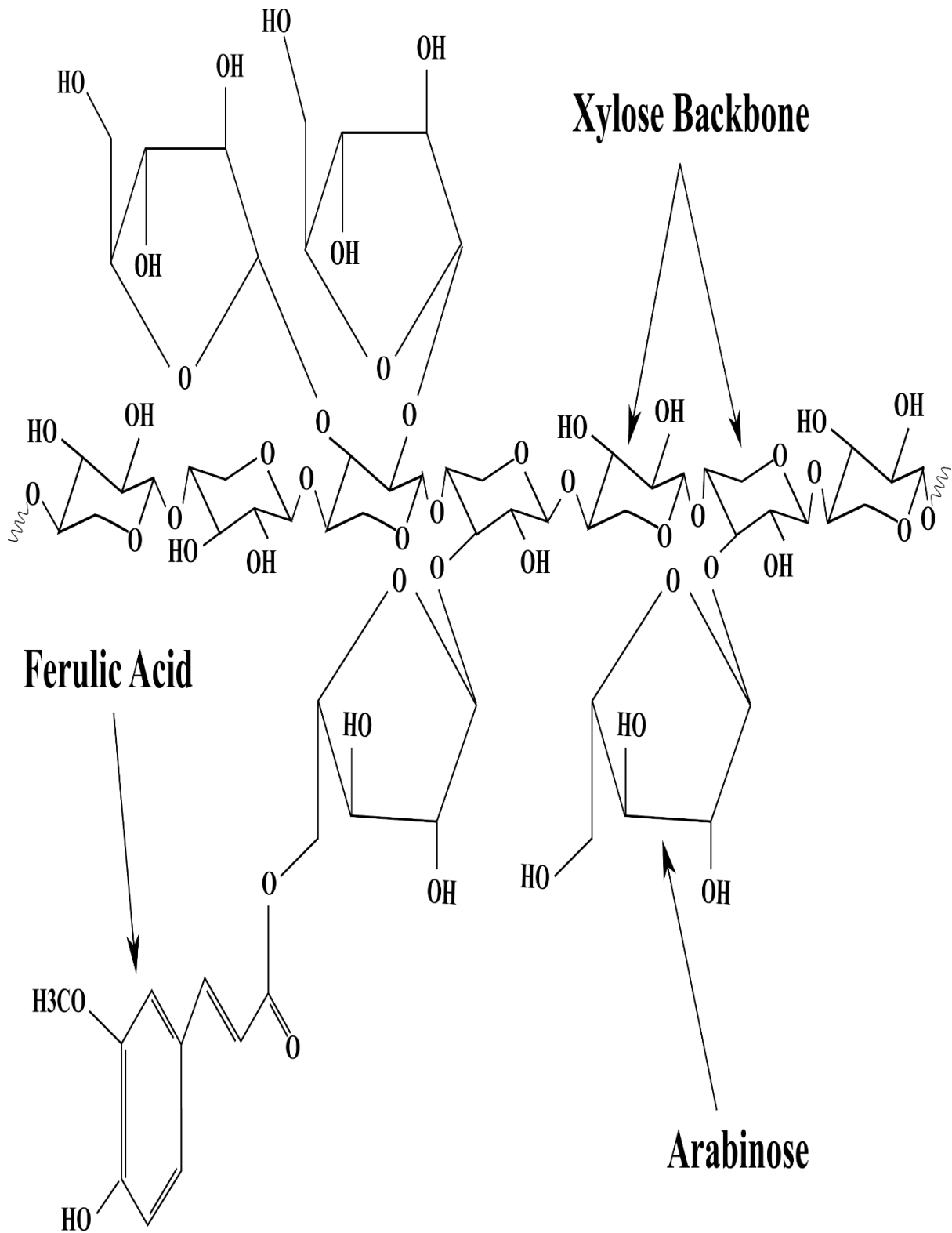
1014

1015 FIGURE 2. Lipopolysaccharide (LPS) structure

1016 a. LPS lipid A, O-antigen and core oligosaccharide. b. TLR4-MD2-CD14 receptor complex. Source. Miller et al.

1017 (2005).

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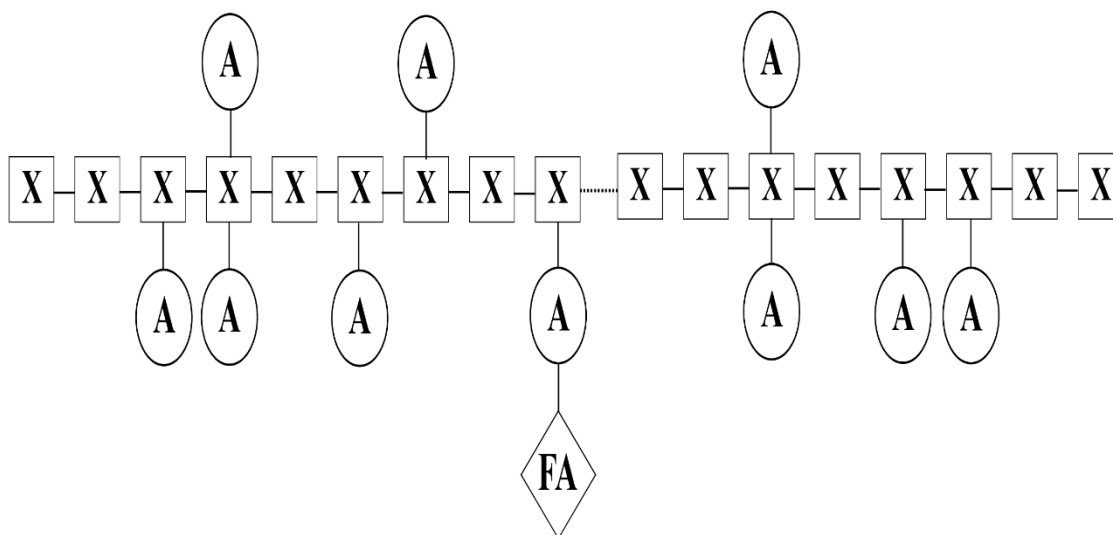
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1020 FIGURE 3 Arabinoxylan structure. Source. Garófalo, Vazquez , Ferreira and Soule (2011).

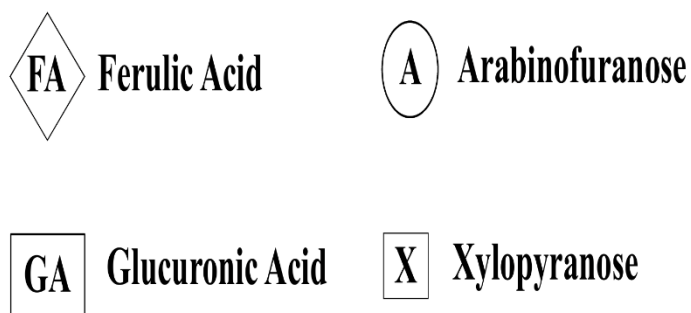
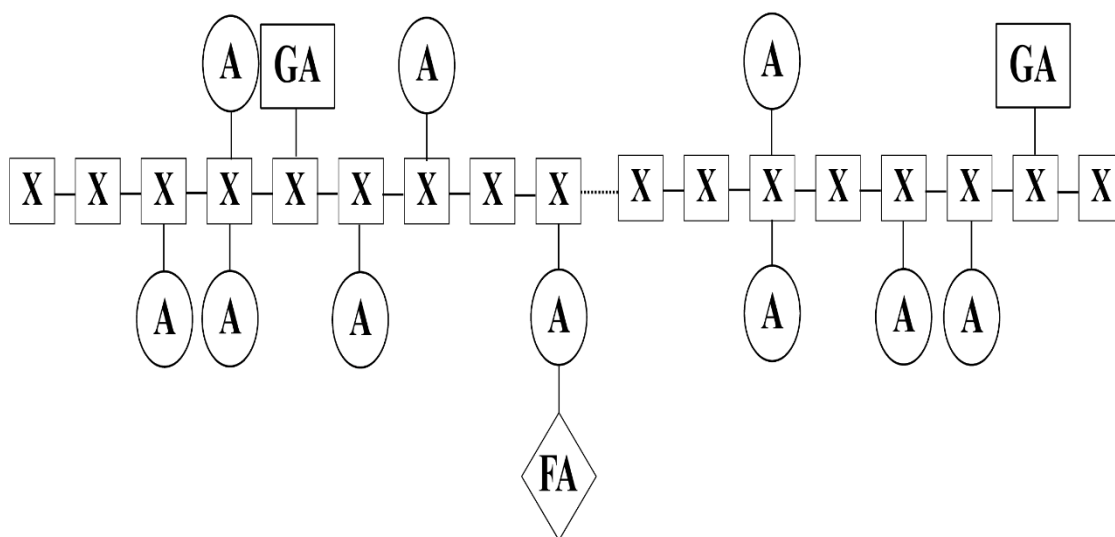
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a



b



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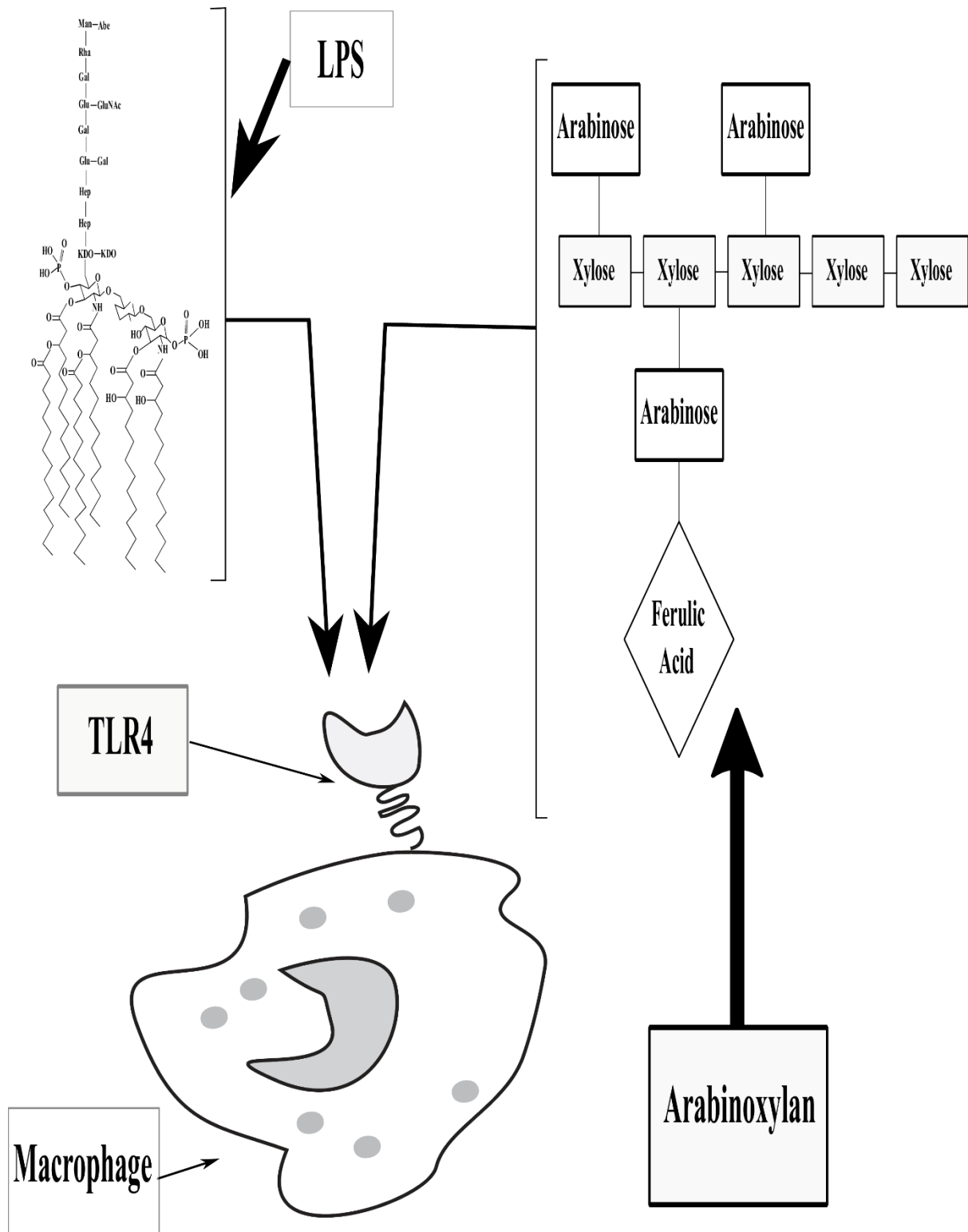
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FIGURE 4 Simplified schematic representation of arabinoxylans AXs. (a) Wheat flour and (b) Wheat bran. Substituents above and below the backbone represent C (O)-2 and C (O)-3 positions, respectively. Source. Edwards, Chaplin, Blackwood, and Dettmar (2003), Qiu et al. (2017), and Zhou et al. (2010)



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

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