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Arabinoxylans from rice bran and wheat immunomodulatory potentials: A Review Article

Abstract

Purpose - The purpose of this review is to discuss recent research on arabinoxylans from rice bran and wheat by-products and their immunomodulatory potential. Also, a potential receptor for arabinoxylans is proposed in relation to arabinoxylan structure.

Design/methodology/approach - This review summarises recent publications on arabinoxylans from rice bran and wheat, classification of arabinoxylans, a brief background on their methods of extraction, and their immunomodulatory potential as they induce proinflammatory responses in vitro, in vivo and humans. The mechanism of action by which arabinoxylans modulate immune activity has yet to be discovered, however, we have proposed a potential receptor for arabinoxylans in relation to arabinoxylans' structure and molecular weight.

Findings - The effects of arabinoxylans from rice bran and wheat on the immune response was found to cause a pro-inflammatory response in vitro, in vivo and humans. In addition, the immune response depends on their structure, the degree of branching and origin.

Originality/Value - This review paper focuses on the effects of arabinoxylans from rice bran and wheat on immunomodulatory potential in vitro, in vivo and humans. A new mechanism of action has been proposed based on the literature and via the link between arabinoxylan and lipopolysaccharide structures, molecular weight and a proposed receptor, which might be activated via both molecules.

Keywords: Arabinoxylans; dietary fibre; non-starch polysaccharides; rice bran, wheat

Introduction

Cereal grains contain variable amounts of non-starch polysaccharide (NSP), namely cell wall material. Cereal grains are composed of hemicelluloses, celluloses, and other materials such as lignins and pectins, and collectively are known as dietary fibre (Comino et al., 2016, Ma et al., 2017)

Arabinoxylans (AXs) are the main NSP constituents of many cereals, and they are predominantly found in the outer layers (bran) and starchy endosperm (flour) (Zhou et al., 2010, Haile et al., 2017). AXs are found in many cereals such as maize, rye, barley, oats, sorghum, wheat and rice. They constitute about 1.37-2.06% of the wheat endosperm (Li et al., 2015). Whereas, in rice they constitute about 4.84-8.5% of the bran (Hashimoto et al., 1987a)

Studies have suggested that AXs extracted from different cereals may have desirable biological effects (Li et al., 2015). Other studies found that AXs extracted from enzymatically modified rice bran, MGN 3 with a low molecular weight, can stimulate both the adaptive and innate immune systems by enhancing dendritic cell maturation, macrophage phagocytosis, and natural killer cell activity (Ghoneum and Matsuura, 2004). On the other hand, AXs extracted from rice bran, without any enzyme pre-treatment, have shown anti-complementary and anti-inflammatory activities in vitro (Wang et al., 2008, Hoshino et al., 2010). Recently, a study showed that AXs from wheat endosperm have the potential to induce nitric oxide (NO) production and interleukin 8 (IL-8) in a dose-dependent manner from U937 and Caco-2 cell lines (Li et al., 2015). The immunomodulatory properties of AXs from different sources have been reported to act as pro-inflammatory and/or anti-

inflammatory which is strongly related to promote or supress growth of cancer cells (Zamarron and Chen, 2011).

In this review, we aim to provide an overview of the immunomodulatory potential of AXs from rice bran and wheat, as they are rich in AXs. We also propose a potential receptor for AXs to which AXs might bind to prior immunomodulatory activities.

Arabinoxylans (AXs)

The NSPs are indigestible by human gut enzymes and are therefore referred to as dietary fibre. NSP makes up 75% of the cell wall and is composed of glucomannan, (1-3) (1-4) β glucan, cellulose and arabinoxylans (pentosans) (Pedersen et al., 2014). Pentosans or arabinoxylans are the major hemicellulosic polysaccharides in cereals, and they make up more than 80% of the NSP in wheat and 10% of rice bran (Malathi and Devegowda, 2001, Mansberger et al., 2014).

Arabinoxylans are the major NSPs found in many cereals and are composed of backbone chains of β-(1-4)-linked D-xylopyranosyl residues to which α-L-arabinofuranose units are linked as side chains in the second and/or third carbon-positions (Courtin et al., 2000, Roubroeks et al., 2000, Zhou et al., 2010). Figure 1 shows the structure of AXs (Izydorczyk and Biliaderis, 1995).

AXs are classified as either water-extractable AXs or water-unextractable AXs (Moers et al., 2005, Malunga and Beta, 2015, Moza and Gujral, 2017). It has been reported that AXs in rye are part of the CWM and they are bound covalently and non-covalently to other CWMs such as proteins, cellulose or lignin. In contrast, AXs in wheat are loosely bound to the surface of the cell wall (Merali et al., 2016). Sasaki

et al. (2000) suggested that the difference in water extractability of AXs in cereals is due to the degree of cross-linking with other CWMs. These cross-links can be covalent ester bonds between the carboxylic acid group of uronic acids and AXs hydroxyl groups or di-ferulic acid bridges between adjacent AXs chains (Fry, 2004, Qiu et al., 2017). It has been reported that wheat endosperm contains between 31 and 111 mg/100g ferulic acid (Michniewicz et al., 1990, Acosta-Estrada et al., 2014) whereas, rice bran contains 303 mg/100g (Jung et al., 2007) which might affect AXs' solubility. Recent reports have shown that ferulic acid side chains are esterified to some arabinose residues (Snelders et al., 2013).

Moreover, these cross-links make extraction of AXs challenging and there is a need to use other treatments such as enzymes, alkali solutions or mechanical methods to effectively remove the AXs from what is a very stable network of covalent and non-covalent crosslinks (Courtin and Delcour, 2001, Jacquemin et al., 2012). The low solubility of AXs could also be due to the close packing of the cell content, which is proposed to be due to steric hindrance (Faulds et al., 2006).

Several studies (Table 1) have shown that the percentage of Water Extractable Arabinoxylans (WEAX) is generally far lower than the Water Un-extractable Arabinoxylans (WUAX). Therefore, increasing and improving WUAX solubility is crucial for those who are interested in converting WUAX to WEAX. It has been reported that treating WUAX with alkali resulted in releasing WUAX from CWM due to the breaking up of bridges between the AXs and the covalent bonds and hydrogen atoms of the CWM (Gruppen et al., 1991, Mansberger et al., 2014). In another study carried out by Courtin and Delcour (2001), the possibility of increasing the extractability of AXs from wheat using enzymes was investigated. WUAX treated

with endoxylanases resulted in an increase in the solubility of AXs due to the degradation of the xylan backbone. Additionally, this led to a reduction in the molecular weight of the extracted AXs fraction (Li et al., 2013). However, there is a limit to the increase in solubility from treating with endoxylanase due to the branched sections, which are not affected by the endoxylanase. On the other hand, several reports show that AXs' solubility depends on the AXs' degree of branching (Mandalari et al., 2005). AXs with high arabinose substitution have a higher solubility in water and vice versa. Arabinoxylans' degree of branching and potential molecular weight distribution determine to a large extent their potential immunological activities (Li et al., 2013, Li et al., 2015, Ma et al., 2017)..

Rice bran AXs (MGN-3/Biobran)

MGN-3/Biobran is an arabinoxylan extracted from rice bran with modification by hydrolysing enzymes from shiitake mushrooms, and its structure is composed of a xylose backbone attached to arabinose monomers with a molecular weight of 30-50 kDa (Ghoneum and Matsuura, 2004, Pérez-Martínez et al., 2015). There are several in vivo, in vitro and human studies suggesting that MGN-3 is capable of enhancing the function of both innate and adaptive immune cells such as B cells, T cells, macrophages, natural killer cells and dendritic cells (Ghoneum and Brown, 1998, Ghoneum and Abedi, 2004, Ghoneum et al., 2004, Ghoneum et al., 2008, Cholujova et al., 2009, Ghoneum and Agrawal, 2014, Badr El-Din et al., 2016a, Badr El-Din et al., 2016b). The mechanism of action of biobran/MGN-3 is not fully understood. However, it has been suggested that modification of the long-chain arabinoxylans is involved and that reducing their molecular weights is important in order for them to be taken up by M cells (microfold cells) in the Peyer's patches. In M cells,

polysaccharides might be transported to the underlying immune cells (Samuelsen et al., 2011). Moreover, it was suggested that low molecular weight AXs can be transferred directly to the blood-stream or can be diffused into the bloodstream through the intestinal walls, and then transported to different immune cells residing in lymph nodes (Ghoneum and Jewett, 1999).

MGN-3 in vitro studies

Several studies have investigated the effect of MGN-3 on different cell lines. It has been reported that MGN-3 is able to transform human monocytes to immature dendritic cells in the presence of two cytokine solutions, LPS and IFNγ and IL-1β, TNFα and IL-6 (Cholujova et al., 2009). MGN-3 showed a substantial (190%) increase in phagocytosis by U937 macrophages. It has also been reported that MGN-3 can increase the IL-6 and TNFα in treated macrophages from U937 and RAW264.7 (murine macrophage cell line) (Ghoneum and Matsuura, 2004, Ghoneum and Agrawal, 2011, Ghoneum and Agrawal, 2014).

Recently, a study showed that MGN-3 can increase the expression of dendritic cells-205 in a dose-dependent manner and it can also increase the production of IL-29 and Type III interferon in human monocyte-derived dendritic cells, suggesting that MGN-3 can efficiently activate dendritic cells. Therefore, MGN-3 might be used for augmenting an efficient immune response against cancer and infections (Ghoneum and Agrawal, 2014).

More recently, treatments with MGN-3 showed a significant increase in NK cell cytotoxicity against several in vitro cells including K562 erythroleukemia, NB1691 neuroblastoma and A673 Ewing sarcoma (Pérez-Martínez et al., 2015).

Furthermore, another study showed that MGN-3 caused inhibition of 34% of human neutrophil HL-60 cells. It also induced phagocytosis in a concentration-dependent manner.

MGN-3 in vivo studies

Several in vivo studies have investigated the functionality of MGN-3 on animal immune systems. Badr El-Din et al. (2008) investigated the effect of intra-tumoural and intra-peritoneal supplementation of MGN-3 on Ehrlich carcinoma-bearing mice, reporting that a concentration of 40 mg/kg body weight of MGN-3 can delay tumour growth. The inhibitory effect of MGN-3 treatment on tumour growth had positive effects from day 14 post-injection, with tumour weight and volume reducing by 45% and 63% respectively in mice at day 35. Moreover, MGN-3 showed antitumour effects and an increase in IFNγ production by 154%, apoptotic activity of 76%, TNFα secretion of 11% and NK cell activity of 100%. These results suggested that the antitumour effect of MGN-3 is due to its ability to induce IFNγ and TNFα.

Recently, a study investigated the effect of MGN-3 on NOD-Scid IL-2 rgunull mice. It was found that there was a significant neuroblastoma growth inhibition in cells treated with MGN-3 (Pérez-Martínez et al., 2015). A more recent study examined the ability of MGN-3 to enhance the apoptosis of tumour cells in mice bearing Ehrlich ascites carcinoma (EAC). It was found that inhibition of tumour growth after MGN-3 treatment was associated with an increase in apoptosis and DNA damage of tumour cells, as well as a decrease in cancer cell proliferation. Their findings suggest that supplementation of MGN-3 can enhance tumour cell demise (Badr El-Din et al., 2016a).

MGN-3 human studies

Several in vitro and in vivo studies have been conducted to investigate the biological activities of MGN-3. However, only a few studies have examined MGN-3 effects in humans. Ghoneum and Jewett (1999) conducted the first human trial on twenty-four healthy subjects for two months. They found that MGN-3 ingestion enhanced NK cell activity against two cancer cell lines (K562 and Raji). This effect was concentration-dependent and the highest response was observed at 46 mg/kg/day of MGN-3. Moreover, NK cells' binding capacity was increased by 310% after one month of MGN-3 oral administration at (45 mg/kg per day) which also confirms the immunoenhancing activity MGN-3 has against tumour cell lines.

In another study conducted by Ghoneum and Brown (1998), 32 cancer patients ingested 3g of MGN-3 every day for a month. It was found that the ingestion of MGN-3 significantly improved NK cell cytotoxicity by a 10-fold. Moreover, MGN-3 enhanced B cell and T cell function in all cancer patients throughout measuring proliferation activity of B and T cells against several mitogens. Furthermore, no hypo-responsiveness in patients was observed post treatment, suggesting MGN-3 is nontoxic, and its use could be encouraged in conjunction with chemotherapy in order to dampen the effect of immunosuppression.

Recently, in a study conducted in 32 multiple myeloma patients, MGN-3 was administered on a daily basis for 3 months. It was demonstrated that MGN-3-treated patients had higher NK activity compared to the placebo group. Moreover, the level of myeloid dendritic cells had significantly increased, suggesting MGN-3 may participate in activation of the innate immunity of multiple myeloma patients (Cholujova et al., 2013). The immunomodulatory potential of MGN-3 is well

documented in vitro, in vivo and humans. However, MGN-3 is a modified form of AXs from rice bran, and there is limited research on the non-modified rice bran AXs and other polysaccharides.

Immunomodulatory effects of rice bran polysaccharides

There is a limited research on the polysaccharides extracted from rice bran without modification, including AXs. In 2008, Wang et al. studied the effect of a rice bran hetero-polysaccharide (RBPS2a) extracted with hot water on anti-complementary activity. The study indicated that RBPS2a has the ability in vitro to induce red blood cell lysis and complement consumption through residual complement activity (Wang et al., 2008). Another study extracted different fraction of arabinoxylan from rice bran using carbohydrate hydrolysing enzymes for a longer period. The extracted arabinoxylan had a low molecular weight and structure similar to MGN-3. Mast cells treated with the arabinoxylan (0.3 mg/ml) showed a remarkable depletion in β-hexosamindase secretion post-antigen stimulation. In addition, IL-4 and TNF-α secretion were inhibited after treating the mast cells with the arabinoxylan, proposing that AXs extracted from rice bran have the ability to suppress cytokine secretion and degranulation of mast cells (Hoshino et al., 2010).

In a recent study, feruloylated AXs from rice bran induced IL-6, IL-1β, prostaglandin E2 (PGE2), NO and TNF-α in RAW264.7 macrophages, suggesting that feruloylated AXs may be able to enhance innate immunity and protect against chronic inflammatory diseases (Fang et al., 2012).

More recently, Wang et al. (2016b) investigated the effect of rice bran polysaccharides on NO and TNF α production in RAW264.7 macrophages. Their

results suggest that the antitumour activity of rice bran polysaccharides is mediated through macrophage activation which in turn induces the secretion of NO and TNF α in a dose-dependent manner.

Immunomodulatory effects of wheat bran and wheat endosperm arabinoxylans

It has been reported that oral administration of AXs extracted from wheat bran using xylanases and alkali extraction have an immune-modulatory effect on both the innate and adaptive immune system (Zhou et al., 2010, Cao et al., 2011).Alkali-extracted arabinoxylans from wheat bran showed an inhibitory effect on tumour growth and IL-2 production at 100-400 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 of AXs (Cao et al., 2011).

Another study conducted by Zhou et al. (2010) indicated that 200 mg/kg oral administration of enzyme-extracted wheat bran AXs exhibits immune-stimulatory effects on both innate and adaptive immunity. The enzyme-extracted AXs (AXE) were reported to stimulate phagocytosis by macrophages and postpone hypersensitivity more than alkaline-extracted arabinoxylans (Zhou et al., 2010).

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

It is clear that there are several factors affecting the immunomodulatory potential of AXs including the method of extraction, enzyme/chemical treatments and botanical source. It is well documented that AXs from different sources have immunomodulatory activities. However, to date, AXs' cellular mechanism of action is not well-investigated Therefore, we will propose a potential receptor for AXs that might provide new insights into AXs' mechanism of action.

Potential arabinoxylan receptors

Previous studies suggested that AXs from different sources have immunomodulatory potential and it is possible to speculate that their mechanism of action is by acting like Pathogen-associated Molecular Patterns (PAMPs). Fascinatingly, extracted AXs from cornhusk and rice bran have shown some similarities in terms of molecular weight and structure to lipopolysaccharide (LPS) from Gram-negative bacteria (Ghoneum and Ogura, 1999, Ogawa et al., 2005). As an example, LPS has in its outer core hexoses such as glucose and galactose, which are found in AXs. Another similarity is that the structure of LPS and AXs includes C-3 branched polysaccharides (Rietschel et al., 1994, Heinrichs et al., 1998). Figure 2 shows the structure of LPS (Miller et al., 2005). Moreover, enzyme-treated AXs from wheat endosperm pentosan had low molecular weights (1-25 kDa) (Li et al., 2015) which are within the molecular weight range (10-20 kDa) of LPS (Mangoni et al., 2008). Therefore, AXs might activate phagocytes by attaching to Toll-like receptors expressed on the surface of phagocytes. Since LPS binds to TLR4 specifically, it suggests that TLR4 may also be a potential receptor for AXs. If true, AXs may compete with LPS for the TLR4 receptor in the presence of infection, thus mediating the LPS-induced immune response. Figure 3 shows a simplified

overview of the potential arabinoxylan receptor and how it might work on the LPS receptor.

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

Structure-activity relationship

It has been suggested that the activity of AXs is dependent on their sugar compositions, molecular weight and degree of branching (Zhou et al., 2010, Cao et al., 2011, Mendis et al., 2017). The most investigated type of AXs (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 AXs (Zhou et al., 2010). Both of the polysaccharides showed the ability to activate the macrophages. However, MGN-3 appeared to be more effective,, which might be due to differences in the sugar composition since MGN-3 has more glucose and galactose side chains (Zhang et al., 2015). In contrast, alkaline-extracted arabinoxylans from wheat bran and banana peel showed substantial immunomodulatory activity, despite the molecular weight of the AXs being large, 288 and 352 kDa, in banana peel and wheat bran respectively, suggesting several receptors may be involved (Zhang et al., 2008, Zhou et al., 2010, Cao et al., 2011). Table 2 shows the relationship between the structural properties of AXs from different sources on immunomodulatory activities.

Conclusions

AXs are important dietary fibres found in many cereals. Arabinoxylans from rice bran and wheat have been reported to modulate the immune responses. Several in vitro, in vivo and human trials have demonstrated the immunomodulatory potential of AXs from rice bran and wheat. The mechanism of action has yet to be discovered. The conclusion from the literature indicates that the biological activities of AXs are associated with several factors such as the source of AXs, their degree of branching and their molecular weight. Moreover, there are structural similarities between LPS from Gram-negative bacteria and AXs, which suggest that LPS and AXs might share the same receptor. Thus, future studies should focus on investigating of the AXs and to not be limited to one receptor only as other receptors might contribute as well. Furthermore, future studies should also focus on studying the molecular structure of AXs and how this affects their immunomodulatory properties.

Conflict of interest

The authors declare no conflict of interest.

References

ACOSTA-ESTRADA, B. A., GUTIÉRREZ-URIBE, J. A. & SERNA-SALDÍVAR, S. O. 2014. Bound phenolics in foods, a review. Food chemistry, 152, 46-55.

BADR EL-DIN, N. K., ABDEL FATTAH, S. M., PAN, D., TOLENTINO, L. & GHONEUM, M. 2016a. Chemopreventive Activity of MGN-3/Biobran Against Chemical Induction of Glandular Stomach Carcinogenesis in Rats and Its Apoptotic Effect in Gastric Cancer Cells. Integrative cancer therapies, 15, NP26-NP34.

BADR EL-DIN, N. K., ALI, D. A., ALAA EL-DEIN, M. & GHONEUM, M. 2016b. Enhancing the Apoptotic Effect of a Low Dose of Paclitaxel on Tumor Cells in Mice by Arabinoxylan Rice Bran (MGN-3/Biobran). Nutrition and cancer, 68, 1010-1020.

BADR EL-DIN, N. K., NOAMAN, E. & GHONEUM, M. 2008. In vivo tumor inhibitory effects of nutritional rice bran supplement MGN-3/Biobran on Ehrlich carcinoma-bearing mice. Nutrition and cancer, 60, 235-244.

CAO, L., LIU, X., QIAN, T., SUN, G., GUO, Y., CHANG, F., ZHOU, S. & SUN, X. 2011. Antitumor and immunomodulatory activity of arabinoxylans: A major constituent of wheat bran. International Journal of Biological Macromolecules, 48, 160-164.

CHOLUJOVA, D., JAKUBIKOVA, J., CZAKO, B., MARTISOVA, M., HUNAKOVA, L., DURAJ, J., MISTRIK, M. & SEDLAK, J. 2013. MGN-3 arabinoxylan rice bran modulates innate immunity in multiple myeloma patients. Cancer Immunology, Immunotherapy, 62, 437-445.

CHOLUJOVA, D., JAKUBIKOVA, J. & SEDLAK, J. 2009. BioBran-augmented maturation of human monocytederived dendritic cells. Neoplasma, 56, 89.

COMINO, P., COLLINS, H., LAHNSTEIN, J. & GIDLEY, M. J. 2016. Effects of diverse food processing conditions on the structure and solubility of wheat, barley and rye endosperm dietary fibre. Journal of Food Engineering, 169, 228-237.

COURTIN, C. & DELCOUR, J. 2001. Relative activity of endoxylanases towards water-extractable and water-unextractable arabinoxylan. Journal of Cereal Science, 33, 301-312.

COURTIN, C., VAN DEN BROECK, H. & DELCOUR, J. 2000. Determination of reducing end sugar residues in oligo-and polysaccharides by gas–liquid chromatography. Journal of Chromatography A, 866, 97-104.

DODEVSKA, M. S., DJORDJEVIC, B. I., SOBAJIC, S. S., MILETIC, I. D., DJORDJEVIC, P. B. & DIMITRIJEVIC-SRECKOVIC, V. S. 2013. Characterisation of dietary fibre components in cereals and legumes used in Serbian diet. Food chemistry, 141, 1624-1629.

FANG, H.-Y., CHEN, Y.-K., CHEN, H.-H., LIN, S.-Y. & FANG, Y.-T. 2012. Immunomodulatory effects of feruloylated oligosaccharides from rice bran. Food chemistry, 134, 836-840.

FAULDS, C. B., MANDALARI, G., LO CURTO, R. B., BISIGNANO, G. & WALDRON, K. W. 2006. Influence of the arabinoxylan composition on the susceptibility of mono-and dimeric ferulic acid release by Humicola insolens feruloyl esterases. Journal of the Science of Food and Agriculture, 86, 1623-1630.

FRY, S. C. 2004. Primary cell wall metabolism: tracking the careers of wall polymers in living plant cells. New phytologist, 161, 641-675.

GHONEUM, M. & ABEDI, S. 2004. Enhancement of natural killer cell activity of aged mice by modified arabinoxylan rice bran (MGN-3/Biobran). Journal of Pharmacy and Pharmacology, 56, 1581-1588.

GHONEUM, M. & AGRAWAL, S. 2011. Activation of human monocyte-derived dendritic cells in vitro by the biological response modifier arabinoxylan rice bran (MGN-3/Biobran). International journal of immunopathology and pharmacology, 24, 941-948.

GHONEUM, M. & AGRAWAL, S. 2014. MGN-3/Biobran enhances generation of cytotoxic CD8+ T cells via upregulation of DEC-205 expression on dendritic cells. International journal of immunopathology and pharmacology, 27, 523-530.

GHONEUM, M. & BROWN, J. NK immunorestoration of cancer patients by MGN-3, a modified arabinoxylan rice bran (study of 32 patients followed up to four years). 6th International Congress on Anti-Aging and Bio-Medical Technologies, 1998.

GHONEUM, M., HAMILTON, J. & GOLLAPUDI, S. 2004. Modified arabinoxylan rice bran (MGN-3/biobran), potentiates chemotherapy-induced apoptosis in human breast cancer cells. The Journal of Nutrition, 134, 3541S.

GHONEUM, M. & JEWETT, A. 1999. Production of tumor necrosis factor-alpha and interferon-gamma from human peripheral blood lymphocytes by MGN-3, a modified arabinoxylan from rice bran, and its synergy with interleukin-2 in vitro. Cancer detection and prevention, 24, 314-324.

GHONEUM, M. & MATSUURA, M. 2004. Augmentation of macrophage phagocytosis by modified arabinoxylan rice bran (MGN-3/biobran). International journal of immunopathology and pharmacology, 17, 283-292.

GHONEUM, M., MATSUURA, M. & GOLLAPUDP, S. 2008. Modified arabinoxylan rice bran (MGN-3/Biobran) enhances intracellular killing of microbes by human phagocytic cells in vitro. International journal of immunopathology and pharmacology, 21, 87-95.

GHONEUM, M. & OGURA, T. 1999. Immunomodulation of human NK cell activity by marina crystal minerals (MCM), a crystallized mixture of minerals and trace elements from sea water. Nutrition research, 19, 1287-1298.

GRUPPEN, H., HAMER, R. & VORAGEN, A. 1991. Barium hydroxide as a tool to extract pure arabinoxylans from water-insoluble cell wall material of wheat flour. Journal of Cereal Science, 13, 275-290.

HAILE, E., GICHEHA, M., NJONGE, F. K. & ASGEDOM, G. 2017. Determining Nutritive Value of Cereal Crop Residues and Lentil (Lens esculanta) Straw for Ruminants. Sciences, 7, 19-29.

HASHIMOTO, S., SHOGREN, M., BOLTE, L. & POMERANZ, Y. 1987a. Cereal pentosans: their estimation and significance. 3. Pentosans in abraded grains and milling by-products. Cereal Chemistry, 64, 39-41.

HASHIMOTO, S., SHOGREN, M. & POMERANZ, Y. 1987b. Cereal pentosans: their estimation and significance. I. Pentosans in wheat and milled wheat products. Cereal chemistry (USA).

HEINRICHS, D. E., YETHON, J. A. & WHITFIELD, C. 1998. Molecular basis for structural diversity in the core regions of the lipopolysaccharides of Escherichia coli and Salmonella enterica. Molecular microbiology, 30, 221-232.

HOSHINO, Y., HIRASHIMA, N., NAKANISHI, M. & FURUNO, T. 2010. Inhibition of degranulation and cytokine production in bone marrow-derived mast cells by hydrolyzed rice bran. Inflammation research, 59, 615-625.

IZYDORCZYK, M. S. & BILIADERIS, C. G. 1995. Cereal arabinoxylans: advances in structure and physicochemical properties. Carbohydrate Polymers, 28, 33-48.

JACQUEMIN, L., ZEITOUN, R., SABLAYROLLES, C., PONTALIER, P.-Y. & RIGAL, L. 2012. Evaluation of the technical and environmental performances of extraction and purification processes of arabinoxylans from wheat straw and bran. Process Biochemistry, 47, 373-380.

JMARES, D. & STONE, B. 1973. Studies on wheat endosperm I. Chemical composition and ultrastructure of the cell walls. Australian Journal of Biological Sciences, 26, 793-812.

JUNG, E. H., RAN KIM, S., HWANG, I. K. & YOUL HA, T. 2007. Hypoglycemic effects of a phenolic acid fraction of rice bran and ferulic acid in C57BL/KsJ-db/db mice. Journal of agricultural and food chemistry, 55, 9800-9804.

KIM, M. Y., LEE, S. H., JANG, G. Y., PARK, H. J., LI, M., KIM, S., LEE, Y. R., NOH, Y. H., LEE, J. & JEONG, H. S. 2015. Effects of high hydrostatic pressure treatment on the enhancement of functional components of germinated rough rice (Oryza sativa L.). Food chemistry, 166, 86-92.

KOEGELENBERG, D. & CHIMPHANGO, A. F. 2017. Effects of wheat-bran arabinoxylan as partial flour replacer on bread properties. Food Chemistry, 221, 1606-1613.

LI, W., HU, H., WANG, Q. & BRENNAN, C. S. 2013. Molecular features of wheat endosperm arabinoxylan inclusion in functional bread. Foods, 2, 225-237.

LI, W., ZHANG, S. & SMITH, C. 2015. The molecular structure features-immune stimulatory activity of arabinoxylans derived from the pentosan faction of wheat flour. Journal of Cereal Science, 62, 81-86.

MA, J., ADLER, L., SRZEDNICKI, G. & ARCOT, J. 2017. Quantitative determination of non-starch polysaccharides in foods using Gas Chromatography with flame ionization detection. Food Chemistry, 220, 100-107.

MALATHI, V. & DEVEGOWDA, G. 2001. In vitro evaluation of nonstarch polysaccharide digestibility of feed ingredients by enzymes. Poultry Science, 80, 302-305.

MALUNGA, L. N. & BETA, T. 2015. Antioxidant capacity of water-extractable arabinoxylan from commercial barley, wheat, and wheat fractions. Cereal Chemistry, 92, 29-36.

MANDALARI, G., FAULDS, C. B., SANCHO, A. I., SAIJA, A., BISIGNANO, G., LOCURTO, R. & WALDRON, K. W. 2005. Fractionation and characterisation of arabinoxylans from brewers' spent grain and wheat bran. Journal of Cereal Science, 42, 205-212.

MANGONI, M. L., EPAND, R. F., ROSENFELD, Y., PELEG, A., BARRA, D., EPAND, R. M. & SHAI, Y. 2008. Lipopolysaccharide, a key molecule involved in the synergism between temporins in inhibiting bacterial growth and in endotoxin neutralization. Journal of Biological Chemistry, 283, 22907-22917.

MANSBERGER, A., D'AMICO, S., NOVALIN, S., SCHMIDT, J., TÖMÖSKÖZI, S., BERGHOFER, E. & SCHOENLECHNER, R. 2014. Pentosan extraction from rye bran on pilot scale for application in gluten-free products. Food Hydrocolloids, 35, 606-612.

MARCOTULI, I., HSIEH, Y. S.-Y., LAHNSTEIN, J., YAP, K., BURTON, R. A., BLANCO, A., FINCHER, G. B. & GADALETA, A. 2016. Structural Variation and Content of Arabinoxylans in Endosperm and Bran of Durum Wheat (Triticum turgidum L.). Journal of agricultural and food chemistry, 64, 2883-2892.

MENDIS, M., LECLERC, E. & SIMSEK, S. 2017. Arabinoxylan hydrolyzates as immunomodulators in Caco-2 and HT-29 colon cancer cell lines. Food & Function, 8, 220-231.

MERALI, Z., MARJAMAA, K., KÄSPER, A., KRUUS, K., GUNNING, A. P., MORRIS, V. J. & WALDRON, K. W. 2016. Chemical characterization of hydrothermally

pretreated and enzyme-digested wheat straw: An evaluation of recalcitrance. Food chemistry, 198, 132-140.

MICHNIEWICZ, J., BILIADERIS, C. & BUSHUK, W. 1990. Water-insoluble pentosans of wheat: composition and some physical properties. Cereal Chemistry, 67, 434-439.

MILLER, S. I., ERNST, R. K. & BADER, M. W. 2005. LPS, TLR4 and infectious disease diversity. Nature Reviews Microbiology, 3, 36-46.

MOERS, K., CELUS, I., BRIJS, K., COURTIN, C. M. & DELCOUR, J. A. 2005. Endoxylanase substrate selectivity determines degradation of wheat water-extractable and water-unextractable arabinoxylan. Carbohydrate research, 340, 1319-1327.

MOZA, J. & GUJRAL, H. S. 2017. Influence of non-starchy polysaccharides on barley milling behavior and evaluating bioactive composition of milled fractions. Food chemistry, 218, 137-143.

OGAWA, K., TAKEUCHI, M. & NAKAMURA, N. 2005. Immunological effects of partially hydrolyzed arabinoxylan from corn husk in mice. Bioscience, biotechnology, and biochemistry, 69, 19-25.

PAVLOVICH-ABRIL, A., ROUZAUD-SÁNDEZ, O., CARVAJAL-MILLÁN, E., NAVARRO, R. E., ROBLES-SÁNCHEZ, R. M. & BARRÓN-HOYOS, J. M. 2016. Molecular characterization of water extractable arabinoxylans isolated from wheat fine bran and their effect on dough viscosity. LWT-Food Science and Technology, 74, 484-492.

PEDERSEN, M. B., DALSGAARD, S., KNUDSEN, K. B., YU, S. & LÆRKE, H. N. 2014. Compositional profile and variation of distillers dried grains with solubles from various origins with focus on non-starch polysaccharides. Animal Feed Science and Technology, 197, 130-141.

PÉREZ-MARTÍNEZ, A., VALENTÍN, J., FERNÁNDEZ, L., HERNÁNDEZ-JIMÉNEZ, E., LÓPEZ-COLLAZO, E., ZERBES, P., SCHWÖRER, E., NUÑÉZ, F., MARTÍN, I. G. & SALLIS, H. 2015. Arabinoxylan rice bran (MGN-3/Biobran) enhances natural killer cell–mediated cytotoxicity against neuroblastoma in vitro and in vivo. Cytotherapy, 17, 601-612.

QIU, S., YADAV, M. P. & YIN, L. 2017. Characterization and functionalities study of hemicellulose and cellulose components isolated from sorghum bran, bagasse and biomass. Food Chemistry.

RIETSCHEL, E. T., KIRIKAE, T., SCHADE, F. U., MAMAT, U., SCHMIDT, G., LOPPNOW, H., ULMER, A. J., ZÄHRINGER, U., SEYDEL, U. & DI PADOVA, F. 1994. Bacterial endotoxin: molecular relationships of structure to activity and function. The FASEB Journal, 8, 217-225.

ROUBROEKS, J., ANDERSSON, R. & ÅMAN, P. 2000. Structural features of (1→ 3),(1→ 4)-β-D-glucan and arabinoxylan fractions isolated from rye bran. Carbohydrate Polymers, 42, 3-11.

SAHASRABUDHE, N. M., SCHOLS, H. A., FAAS, M. M. & VOS, P. 2016. Arabinoxylan activates Dectin-1 and modulates particulate β-glucan-induced Dectin-1 activation. Molecular nutrition & food research, 60, 458-467.

SAMUELSEN, A. B., RIEDER, A., GRIMMER, S., MICHAELSEN, T. E. & KNUTSEN, S. H. 2011. Immunomodulatory activity of dietary fiber: arabinoxylan and mixed-linked beta-glucan isolated from barley show modest activities in vitro. International journal of molecular sciences, 12, 570-587.

SÁROSSY, Z., TENKANEN, M., PITKÄNEN, L., BJERRE, A.-B. & PLACKETT, D. 2013. Extraction and chemical characterization of rye arabinoxylan and the effect of β-glucan on the mechanical and barrier properties of cast arabinoxylan films. Food hydrocolloids, 30, 206-216.

SASAKI, T., YASUI, T. & MATSUKI, J. 2000. Influence of non-starch polysaccharides isolated from wheat flour on the gelatinization and gelation of wheat starches. Food Hydrocolloids, 14, 295-303.

SNELDERS, J., DORNEZ, E., DELCOUR, J. A. & COURTIN, C. M. 2013. Ferulic acid content and appearance determine the antioxidant capacity of arabinoxylanoligosaccharides. Journal of agricultural and food chemistry, 61, 10173-10182.

WANG, J., SMITS, E., BOOM, R. M. & SCHUTYSER, M. A. 2015. Arabinoxylans concentrates from wheat bran by electrostatic separation. Journal of Food Engineering, 155, 29-36.

WANG, J., SUO, G., DE WIT, M., BOOM, R. M. & SCHUTYSER, M. A. 2016a. Dietary fibre enrichment from defatted rice bran by dry fractionation. Journal of Food Engineering, 186, 50-57.

WANG, L., LI, Y., ZHU, L., YIN, R., WANG, R., LUO, X., LI, Y., LI, Y. & CHEN, Z. 2016b. Antitumor activities and immunomodulatory of rice bran polysaccharides and its sulfates in vitro. International journal of biological macromolecules, 88, 424-432.

WANG, L., ZHANG, H., ZHANG, X. & CHEN, Z. 2008. Purification and identification of a novel heteropolysaccharide RBPS2a with anti-complementary activity from defatted rice bran. Food chemistry, 110, 150-155.

ZAMARRON, B. F. & CHEN, W. 2011. Dual roles of immune cells and their factors in cancer development and progression. International journal of biological sciences, 7, 651.

ZHANG, S., LI, W., SMITH, C. & MUSA, H. 2015. Cereal-derived arabinoxylans as biological response modifiers: extraction, molecular features, and immune-

stimulating properties. Critical reviews in food science and nutrition, 55, 1035-1052.

ZHANG, X.-N., ZHOU, S.-M. & WANG, S.-P. 2008. Optimizing enzymatic hydrolysis conditions of arabinoxylan in wheat bran through quadratic orthogonal rotation combination design. Food Science, 28, 141-145.

ZHOU, S., LIU, X., GUO, Y., WANG, Q., PENG, D. & CAO, L. 2010. Comparison of the immunological activities of arabinoxylans from wheat bran with alkali and xylanase-aided extraction. Carbohydrate Polymers, 81, 784-789.

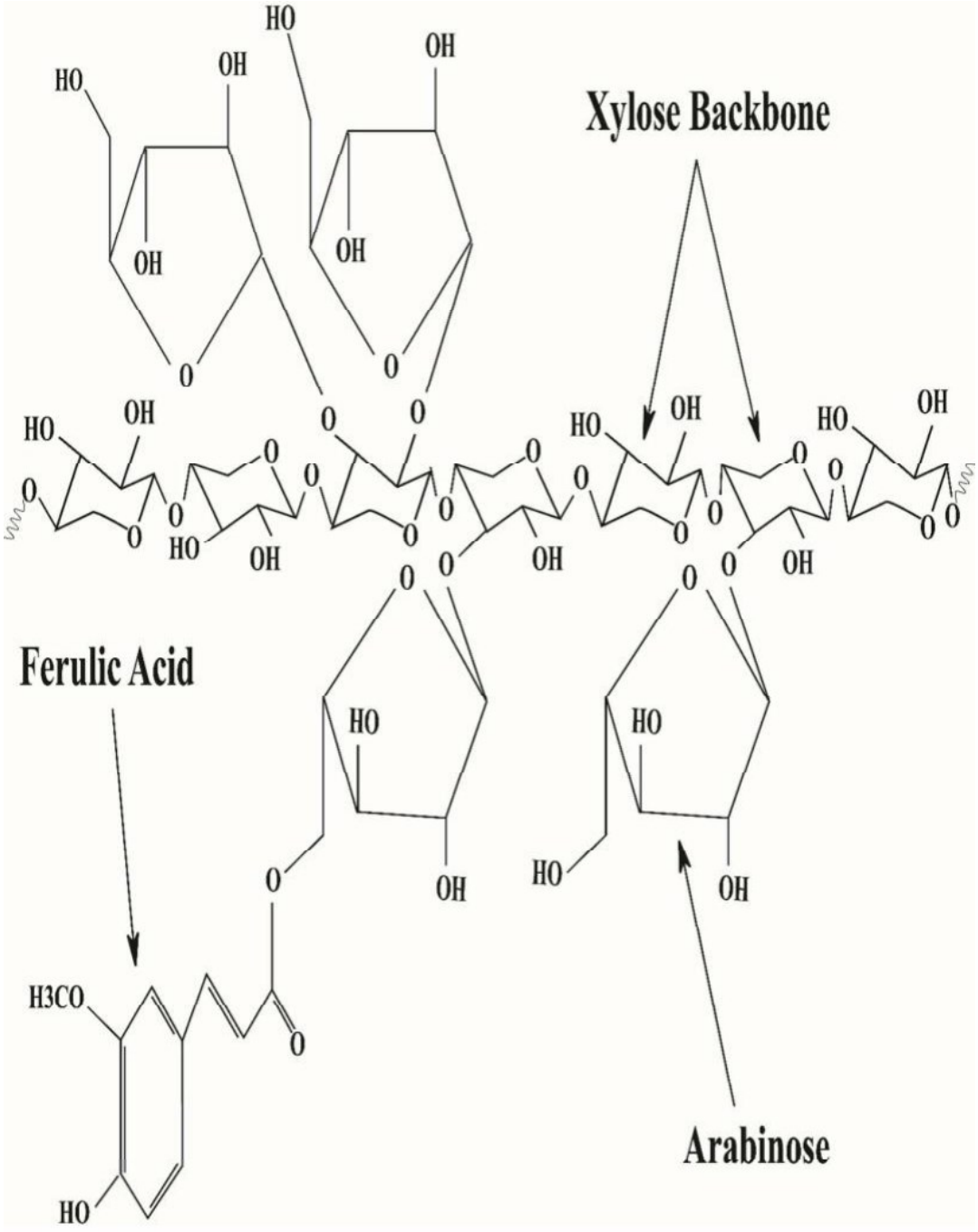

Figure 1. Arabinoxylan structure (Izydorczyk and Biliaderis, 1995).

Arabinoxylan structure is composed of backbone chains of β-(1-4)-linked D-xylopyranosyl residues to which α-L-arabinofuranose units are linked as side chains in the second and/or third carbon-positions.

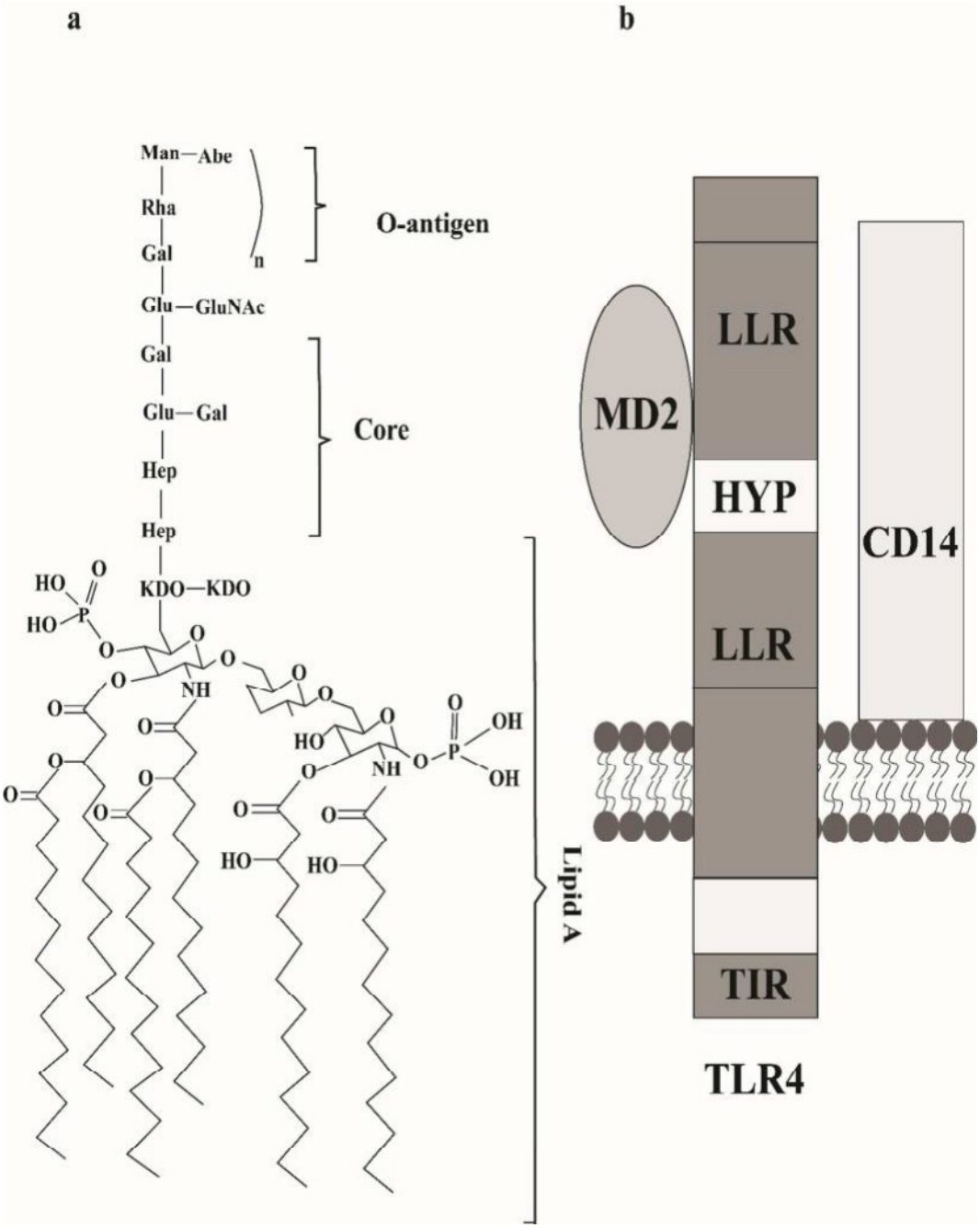

Figure 2. Lipopolysaccharide (LPS) structure

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

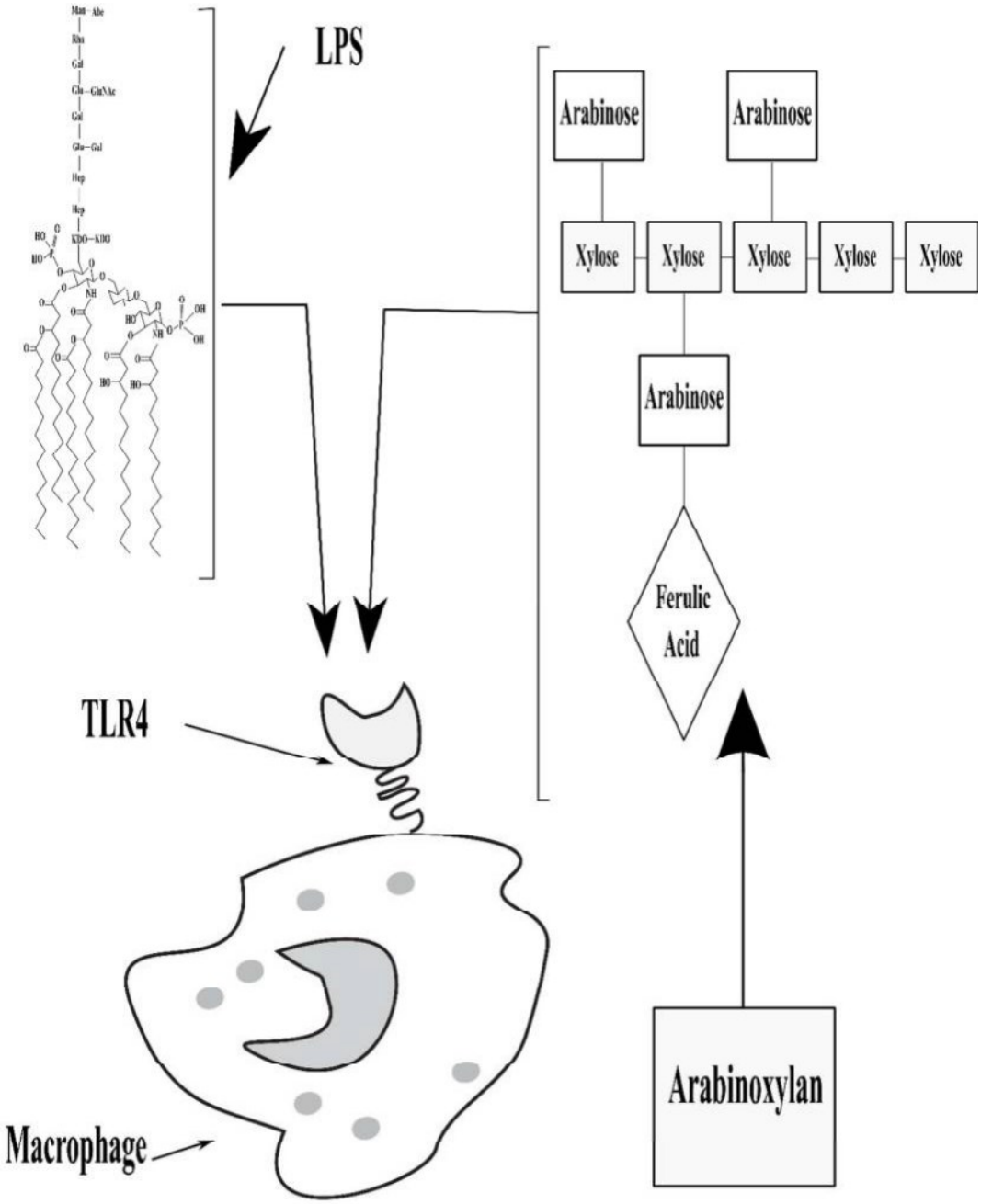

Figure 3. Simplified representation of the macrophage TLR 4 receptor with AXs and LPS

AXs might compete with LPS on TLR4 receptor of macrophages, in which the immune response will be modulated.

Table 1. Water extractable and water-unextractable AXs in rice and wheat (dry weight basis) weight basis

WEAX and WUAX in some cereal grains and cereal by-products (dry weight basis)					
Cereal	Tissues	Total AXs%	WEAX%	WUAX%	References
Rice	Defatted pericarp	26.7	NA	NA	(Wang et al., 2016)
	Defatted aleurone	13.2	NA	NA	(Wang et al., 2016)
	Cooked	0.5	NA	NA	(Dodevska et al., 2013)
	Germinated whole grain	2.97-6.84	NA	NA	(Kim et al., 2015)
Wheat	De-starched bran	29.1	NA	NA	(Koegelenberg and Chimphango, 2017)
	Bran	26.2	NA	NA	(Koegelenberg and Chimphango, 2017)
	Bran	23	NA	NA	(Wang et al., 2015)
	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)
	White flour	5.1	2.1	2.96	(Pavlovich-Abril et al., 2016)
	Bran	13	2.86-4.29	8.71-10.14	(Sárossy et al., 2013)
	Bran	26	0.71	25.29	(Zhang et al., 2016b)

Table2. Structural properties of AXs

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)

Structural properties of AXs in relation to the extraction method and immunomodulatory activity in rice bran and wheat bran