

Table 1-Studies carried on whole grain-odd chain phenolic lipid- alkylresorcinols (ARs) at Carleton University since 2011

Sample	Main analysis-focus	Outcomes	References
Six fractions of rye bran (cultivar <i>Hazlet</i> and RT202 genotype)	ARs content, composition, ORAC, GC-MS, PC-12 AC cell line (MTT assay), TPC.	Total amount of ARs decreases from the outermost to innermost fractions similar to ORAC values. A positive correlation between GC-MS results. Higher AR content provides higher protection against free radical damage.	(Gliwa, Gunenc, Ames, Willmore, & Hosseini, 2011)
Triticale bran	Male CF-1 mice (n=40) fed with high fat diet; glucose tolerance test (GTT), SOD, MRI, Bradford, ORAC, GSH, GC-MS	ARs may serve as a preventive measure against oxidation linked with high fat diet and obesity	(Agil, Patterson, Mackay, Abizaid, & Hosseini, 2016)
Wheat bran from six cultivars grown in four different regions	ARs composition, GC-MS, antioxidant activity (DPPH, ORAC and TPC)	Location and cultivar affect total ARs composition, and their antioxidant activity	(Gunenc, HadiNezhad, Tamburic-Ilincic, Mayer, & Hosseini, 2013a)
Wheat bran	Green and solvent extraction of ARs, composition analysis, HPLC, antioxidant activity	Solvent extraction yielded more ARs than supercritical CO <sub>2</sub> ; Solvent, cultivar, and their interactions had significant effects on ARs composition, and antioxidant activity	(Gunenc, HadiNezhad, Farah, Hashem, & Hosseini, 2015)
<i>Portulaca oleracea</i> seeds	ARs composition; lipid composition; germination effects; antioxidant activity	The presence of alkylresorcinols is demonstrated in purslane seeds.	(Gunenc, Rowland, Xu, Marangoni, & Hosseini, 2019)
Wheat bran	Stability of ARs in four different formulated bread; composition, antioxidant activity	Provide new knowledge on the alkylresorcinols stability in WB during baking	(Gunenc et al., 2013b)
Phenolic lipid	Review the potentials of phenolic lipids in preventing Alzheimer's disease	Highlights the pathways and mechanisms associated with the pathogenesis of Alzheimer's disease; the modulatory effects of phenolic lipids on these pathways.	(Meshginfar, Tavakoli, Dornan, & Hosseini, 2020)
Whole grain cereals	Review the bioactivity of alkylresorcinols	Gives background info about the ability of ARs to reduce or inhibit triglyceride accumulation, tumor cell formation, thromboxane synthesis, and enhance	(Agil & Hosseini, 2012)

		liposome stability, cardiovascular disease prevention as well as liposomal drug delivery	
Triticale bran	ARs extraction optimization; composition analysis, HPLC	The response surface methodology (RSM) used to optimise experimental conditions for ARs extraction.	(Agil, Oomah, Mazza, & Hosseinian, 2012)

Table 2. Proof of concept-studies in alkylresorcinols bioactivity

Source	Study focus	Study design	Outcome	Reference
Whole-grain wheat and whole-grain rye	Type 2 diabetes	932 case-control pairs	Whole-grain intake dominated by rye (indicated by plasma AR C17/C21 ratio) inversely associated with T2D	(Biskup et al., 2016)
Wheat bran	Type 2 diabetes	C57BL/6J mice fed with 0.4% ARs	ARs increase glucose tolerance and insulin sensitivity by suppressing hepatic lipid accumulation and intestinal cholesterol absorption	(Oishi et al., 2014)
Whole grain rye	Metabolic syndrome	30-65 years of age Nordic people (n=95) with metabolic syndrome without diabetes; diet high in whole grain at 18/24 weeks	The AR C17/C21 ratio was inversely associated with fasting insulin concentration, and positively linked with insulin sensitivity indices. This ratio is associated with increased insulin sensitivity in a population with metabolic syndrome	(Magnusdottir et al., 2014)
Hexylresorcinol solution	Insulin absorption	Intestinal loops of anesthetised dogs; administered a solution of ARs and insulin	ARs increased the absorption of insulin from the gastrointestinal tract and into the circulating bloodstream, significantly dropped blood glucose levels; could be due to its surface-tension lowering effect at the intestinal mucosa	(Sealock, Murlin, & Driver, 1993)
Whole grain cereal products	Antioxidant activities	Rye bran ARs(C15-C25) and extracts from whole grain cereal products: DPPH;CL:	Values of EC <sub>50</sub> for all the ARs homologues (5 to 300 µM) were higher than Trolox, and α-, δ-, and γ-tocopherols.	(Koryciński, Czelna, Jaromin, & Kozubek, 2009)
<i>Lithraea molleoides</i>	Antioxidant activities	Dichloromethane extract (DM) of the plant and isolated cytotoxic 5-alkyl resorcinol derivative, 1,3-dihydroxy-5-(tridec-4',7'-dienyl) benzene on the proliferation of tumoral and normal lymphocytes	Dichloromethane extract might be a crucial antioxidant source and immunomodulatory compounds, and suggested to be studied on cancer diseases.	(López, Ferraro, & Anesini, 2010)
5-n-alkylresorcinols	Antigenotoxic & antioxidant activity	HT29 cells incubated with ARs homologues; DNA damage;	ARs inhibited copper-mediated oxidation of human LDL in vitro; ARs exhibit antigenotoxic and	(Parikka, Rowland, & Salonen, 2000)

		comet assay	antioxidant activity <i>in vitro</i>	Welch, & Wähälä, 20
5-Heptadecylresorcinol (AR-C17)	Bioactivity of AR-C17	Neuroprotective effect & potential defense mechanisms against (H <sub>2</sub> O <sub>2</sub> )-induced apoptosis and mitochondria dysfunction were investigated in PC-12 cells.	AR-C17 suppressed oxidative damage to cells, and ROS-mediated cells apoptosis	(Liu et al., 2020)
Spelt bran and rye bran	ARs cytotoxicity	Mouse fibroblast cell line L929 were used to test cytotoxicity of ARs	ARs showed lower toxicity than hydroquinone; potential safety use of alkylresorcinols in diet supplements, cosmetics or pharmaceutical products.	(Biskup, Zaczynska, Krauze-Baranowska, Fecka, 201
ARs derived from wheat bran extracts	ARs protection against myofibrillar degeneration	Male C57BL/6N mice were fed with ARs-supplemented diet (0.4%, w/w); PCR; hematoxylin and eosin staining and measurement of cross-sectional area	Dietary supplementation with ARs prevents muscle atrophy through a shift of energy supply	(Hiramoto et al., 2018)
ARs from whole grain	A systematic review of ARs and cancer prevention	Studies in PubMed, Scopus, ProQuest, AEBSCOhost, SpringerLink, ArticleFirst, Taylor&Francis, Wiley Online and ScienceDirect databases.	All reviewed studies showed that ARs are likely to find application in cancer prevention; still there is a need for intervention studies to confirm their preventive action.	(Kruk, Abdo Enein, Bernstein, Marchlewski, 2017)
ARs (whole grain and rye)	A case-control study; Plasma AR metabolite risk of ischemic stroke	Cases (n=990) with first ischemic stroke; plasma DHPPA determined	Plasma metabolites of ARs (DHPPA) were inversely related with ischemic stroke risk.	(Sun et al., 2019)

## References

- Agil, R., & Hosseinian, F. (2012). Bioactivity of alkylresorcinols.
- Agil, R., Oomah, D. B., Mazza, G., & Hosseinian, F. S. (2012). Optimization of alkylresorcinols extraction from triticale bran using response surface methodology. *Food and Bioprocess Technology*, 5(7), 2655-2664. doi: 10.1007/s11947-011-0756-7
- Agil, R., Patterson, Z., Mackay, H., Abizaid, A., & Hosseinian, F. (2016). Triticale bran alkylresorcinols enhance resistance to oxidative stress in mice fed a high-fat diet. *Foods*, 5(1), 5.
- Biskup, I., Kyrø, C., Marklund, M., Olsen, A., van Dam, R. M., Tjønneland, A., et al. (2016). Plasma alkylresorcinols, biomarkers of whole-grain wheat and rye intake, and risk of type 2 diabetes in Scandinavian men and women. *The American Journal of Clinical Nutrition*, 104(1), 88-96. doi: 10.3945/ajcn.116.133496
- Biskup, I., Zaczynska, E., Krauze-Baranowska, M., & Fecka, I. (2017). Evaluation of cytotoxicity of 5-n-alkylresorcinol homologs and fraction on mouse fibroblast cell line L929. *European Food Research and Technology*, 243(7), 1137-1148. doi: 10.1007/s00217-016-2827-5
- Gliwa, J., Gunenc, A., Ames, N., Willmore, W., & Hosseinian, F. (2011). Antioxidant activity of alkylresorcinols from rye bran and their protective effects on cell viability of PC-12 AC cells. *J. Agric. Food Chem*, 59(21), 1473-1482.
- Gunenc, A., HadiNezhad, M., Farah, I., Hashem, A., & Hosseinian, F. (2015). Impact of supercritical CO<sub>2</sub> and traditional solvent extraction systems on the extractability of alkylresorcinols, phenolic profile and their antioxidant activity in wheat bran. *Journal of Functional Foods*, 12, 109-119. doi: <https://doi.org/10.1016/j.jff.2014.10.024>
- Gunenc, A., HadiNezhad, M., Tamburic-Ilincic, L., Mayer, P. M., & Hosseinian, F. (2013a). Effects of region and cultivar on alkylresorcinols content and composition in wheat bran and their antioxidant activity. *Journal of Cereal Science*, 57(3), 405-410. doi: <https://doi.org/10.1016/j.jcs.2013.01.003>
- Gunenc, A., Rowland, O., Xu, H., Marangoni, A., & Hosseinian, F. (2019). Portulaca oleracea seeds as a novel source of alkylresorcinols and its phenolic profiles during germination. *LWT*, 101, 246-250. doi: <https://doi.org/10.1016/j.lwt.2018.10.075>
- Gunenc, A., Tavakoli, H., Seetharaman, K., Mayer, P. M., Fairbanks, D., & Hosseinian, F. (2013b). Stability and antioxidant activity of alkylresorcinols in breads enriched with hard and soft wheat brans. *Food Research International*, 51(2), 571-578. doi: <https://doi.org/10.1016/j.foodres.2013.01.033>
- Hiramoto, S., Yahata, N., Saitoh, K., Yoshimura, T., Wang, Y., Taniyama, S., et al. (2018). Dietary supplementation with alkylresorcinols prevents muscle atrophy through a shift of energy supply. *The Journal of Nutritional Biochemistry*, 61, 147-154. doi: <https://doi.org/10.1016/j.jnutbio.2018.08.014>
- Korycińska, M., Czelná, K., Jaromin, A., & Kozubek, A. (2009). Antioxidant activity of rye bran alkylresorcinols and extracts from whole-grain cereal products. *Food chemistry*, 116(4), 1013-1018. doi: <https://doi.org/10.1016/j.foodchem.2009.03.056>
- Kruk, J., Aboul-Enein, B., Bernstein, J., & Marchlewicz, M. (2017). Dietary alkylresorcinols and cancer prevention: a systematic review. *European Food Research and Technology*, 243(10), 1693-1710. doi: 10.1007/s00217-017-2890-6

- Liu, J., Wang, Y., Hao, Y., Wang, Z., Yang, Z., Wang, Z., et al. (2020). 5-Heptadecylresorcinol attenuates oxidative damage and mitochondria-mediated apoptosis through activation of the SIRT3/FOXO3a signaling pathway in neurocytes. [10.1039/C9FO03028J]. *Food & Function*, 11(3), 2535-2542. doi: 10.1039/c9fo03028j
- López, P., Ferraro, G., & Anesini, C. (2011). Comparative antioxidant activity of an extract of *Lithraea molleoides* and an isolated 5-alkyl resorcinol derivative. Effects on the proliferation of normal and tumoral lymphocytes. . *Phytotherapy research*, 25(2), 271-276. doi: <https://doi.org/10.1002/ptr.3256>
- Meshginfar, N., Tavakoli, H., Dornan, K., & Hosseinian, F. (2020). Phenolic lipids as unique bioactive compounds: a comprehensive review on their multifunctional activity toward the prevention of Alzheimer's disease. *Critical Reviews in Food Science and Nutrition*, 1-10. doi: 10.1080/10408398.2020.1759024
- Oishi, K., Yamamoto, S., Itoh, N., Nakao, R., Yasumoto, Y., Tanaka, K., et al. (2014). Wheat Alkylresorcinols Suppress High-Fat, High-Sucrose Diet-Induced Obesity and Glucose Intolerance by Increasing Insulin Sensitivity and Cholesterol Excretion in Male Mice. *The Journal of Nutrition*, 145(2), 199-206. doi: 10.3945/jn.114.202754
- Parikka, K., Rowland, I. R., Welch, R. W., & Wähälä, K. (2006). In Vitro Antioxidant Activity and Antigenotoxicity of 5-n-Alkylresorcinols. *Journal of Agricultural and Food Chemistry*, 54(5), 1646-1650. doi: 10.1021/jf052486e
- Sealock, R. R., Murlin, J. R., & Driver, R. L. (1939). A COMPARATIVE STUDY OF THE EFFECT OF ALKYLRESORCINOLS AND RELATED COMPOUNDS UPON THE ABSORPTION OF INSULIN FROM ISOLATED INTESTINAL LOOPS OF ANESTHETIZED DOGS. *American Journal of Physiology-Legacy Content*, 128(1), 92-96. doi: 10.1152/ajplegacy.1939.128.1.92
- Sun, T., Zhang, Y., Huang, H., Wang, X., Zhou, L., Li, S., et al. (2019). Plasma alkylresorcinol metabolite, a biomarker of whole-grain wheat and rye intake, and risk of ischemic stroke: a case-control study. *The American Journal of Clinical Nutrition*, 109(2), 1-7. doi: 10.1093/ajcn/nqy323