A Mini Review on Biomarkers of Whole Grain Barley and Whole Grain Wheat Intake*

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Abstract

1 Introduction

Whole grains (WGs) and their processed food could have health beneficial effects. However, epidemiologic studies showed mixed results due to subjective self-report based food exposure measurement[1]. Using Biomarkers of Food Intake (BFIs) can potentially measure food exposure in population more objectively with accuracy and detail[2].

Alkylresorcinols (ARs) and their metabolites were widely reported and validated biomarkers for WGs intake. In plants commonly consumed for food, ARs only present high amounts in rye and wheat, especially concentrated in their bran parts[3]. Therefore, ARs have the possibility to be used as biomarkers for whole grain wheat and rye intake.

Increasing evidence showed that, different WG cereal types (such as wheat, rye, oat and barley etc.) could benefit health differently. However, classical self-reported measurement tools used in observational studies could cause biases and confoundings to distinguish each cereal type. Therefore, discovering BFIs of each whole grain type could potentially provide a tool to accurately quantify their exposures.

This mini-review aimed at systematically examining available literatures to obtain information of potential biomarkers for WG barley and wheat intake. This will prioritize further identification and validation of the thesis work.

2 Materials and Methods

This review referred the systematic BFIRev methodology[4]. The flowchart was included in Appendix (Fig-1)

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The objective of this literature review was to identify and evaluate reported potential biomarkers for dietary assessment for whole grain wheat and whole grain barley.

Keywords as suggested in the guidelines[4] were used to search in 3 database (PubMed, Web of Science, Scopus). Keywords used for searing BFI barley in human: (barley) AND (biomarker* OR marker* OR metabolite* OR biokinetics OR biotransformation OR pharmacokinetics) AND (intake OR meal OR diet OR ingestion OR consumption OR eating OR food) AND (human* OR men OR women OR patient* OR volunteer* OR participant*) AND (trail* or experiment OR study) AND (urine OR plasma OR blood OR serum OR excretion OR hair OR toenail OR faeces OR faecal water). The first element was changed to wheat for wheat intake biomarker searching.

Due to limited amount of searching results, barley searching scope was expanded to animal studies. Therefore, the keyword (animal* OR goat OR sheep OR cow OR mice OR mouse* OR animal model* OR dog*) was used to replace the previous 'human*' subjects. In addition, 'feed' was added to 'food' entry.

Other database including HMDB[5], FoodDB[6], PhenolExplorer[7], Dictionary of Food Compound[8] were also used to explore compounds present only in WG barley and wheat.

In order to verify the uniqueness of compound, the same keywords combinations were used but with compound instead of 'wheat' and 'barley'.

3 Results

3.1 WG barley

The literature search got 129 records after removing duplicate records from merged 3 database search results. However, within them, none of the studies directly investigated WG barley intake biomarkers. This could be explained by limited dietary exposure of barley in population. Although barley is the 4th most produced cereal grains worldwidely. Most of them is used for brewing or feed. Approximately only 4% is directly consumed[9].

When the scope expanded to animal studies, the search results still did not show any direct research about BFIs. Most of studies were interested in how barley feed can benefit the growth of animal or quality improvement of animal-source products[10, 11].

A 2-month intervention study[12] incorporated 75% refined drum wheat and 25% WG barley. The fecal samples showed significant change in microbiota and metabolome after intervention[12]. However, no specific metabolite can indicate WG barley intake.

ARs and their metabolites may not indicate WG barley intake. Several observation studies[13, 14] investigated correlation between ARs metabolites and whole grain intake. Although these studies tried to cover more whole grain species, for example, one study[14] listed 7 types of regularly consumed WGs

in American populations in the Food Frequency Questionnaire (FFQ)[1], barley was not solely listed. Therefore, although ARs and their metabolites got good correlation with these 'Whole-grain intake'. Readers should be cautious to apply these markers to WG barley intake. In addition, ARs concentration in cereal barley is much lower compared with WG wheat and rye, with similar concentration with refined wheat and rye flours (Table-1).

Cereal	Conc. range in cereal	Conc. average or range in WG flour	Conc. average in refined flour	Main homologues	C17:C21 homologues ratio
Rye	360-3200	972	90	C17, C19, C21	0.8-0.9
Wheat	761-8390	490-710	36	C19, C21	0.07-0.1
Barley	55.8-98.2	NA	NA	C19, C21, C25	NA

Table 1: Prensence of ARs in Cereal Grains, adapted from [15–17](unit: µg/g dm), conc. varies due to different species and milling methods.

Most search results focused on barley's *effect biomarkers* as defined by Dragsted[18] and Gao[19], such as bowel health indicators[20], postprandial glucose and insulin response[21], lipid profiles and cardiovascular diseases (CVD) markers[22], etc. However, in these intervention studies, compliance monitoring lacked objective markers.

Further search results in food chemistry, cereal science and plant science showed some compounds exclusively present in barley. These could give hints for further identification. The results were summarized in Table-2.

No	Candidate biomarker	Formula	Chemical group	Presence in Food	Reference
1	Hordenine	$C_{10}H_{15}NO$	alkaloid	germinating barley, beer and other plants	[23]
4	Hordatine A	$C_{28}H_{38}N_8O_5$	alkaloid	only reported in barley	FoodDB (002330)
4	Hordatine B	$C_{29}H_{40}N_8O_5$	alkaloid	only reported in barley	FoodDB (002328)
2	Distichonic acid A	$C_{10}H_{18}N_2O_8$	gamma amino acids and derivatives	only reported in barley	FoodDB (18164)
3	Distichonic acid B	$C_{10}H_{18}N_2O_8$	gamma amino acids and derivatives	only reported in barley	FoodDB (018165)
5	14,16-Nona cosanedione	$C_{29}H_{56}O_2$	ketone	only reported in barley	FoodDB (013891)
6	N-Norgramine	$C_{10}H_{12}N_2$	indole	only reported in barley	FoodDB (017815)

Table 2: Candidate Biomarkers for WG barley intake

To conclude, barley, especially WG barley attracted a lot of interest due to its health beneficial effects for chronic disease. However, due to barley's limited exposure in the population, currently there's no reported biomarkers can indicate its intake. However, a lot of sparse information was reported from

[1]Dark breads, High-fiber or bran cereals, Cooked cereals and grits, Regular granola, Granola bars and cereal bars, Plain popcorn (no butter) or low-fat microwave popcorn, Buttered or gular microwave popcorn

cereal and food chemistry could give hints to identification and validations of WG barley's intake biomarkers.

3.2 WG wheat

The literature search got 312 results after removing duplicate records from merged results. XXX were used.

ARs and their metabolites (3,5-DHPPTA, 3,5-DHPPA, 3,5-DHBA and 3,5-DHBA glycine) were widely reported, validated and applied biomarkers for WG wheat and rye intake. Total ARs were used as biomarkers for overall WGs wheat and rye exposure. In order to distinguish WG wheat and rye. The ratio of C17:0/C21:0 was used. ARs, depending on different milling methods and grain species, varies the concentration and homologues compositions (Table-1). The homologues ratio C17:0/C21:0 was firstly proposed in cereal science to distinguish WG rye and wheat[24]. Further, the ratio was also proposed as an biomarker to indicate which cereal dominates in the diet: if the ratio is close to 1.0, rye dominated; close to 0.1, wheat dominates[25, 26].

Dietary factor	No. subjects	Study design	Sample type	Analytical method	Candidate biomarker(s)	Reference
WG wheat WG rye	39	intervention, cross-over, randomized	plasma	GC-MS	AR C17:0/C21:0	[25]
Healthy new nordic diet[2]	166	intervention, parallel, randomized, multi-center (18/24 weeks)	plasma	GC-MS	AR C17:0/C21:0	[27]
WGs[3]	266	randomized, parallel-group, intervention	plasma	GC-MS	Total ARs	[28]

Table 3: Potential Biomarkers of Wheat Intake in Intervention study

Type of WG	No. subjects	Sample type	Analytical method	Candidate biomarker(s)	Associated with	Reference
WGs[4]	104	spot urine	GC-MS	ARs metabolites (DHBA, DHPPA)	FFQ	[29]
WGs[5]	2845	fasting and non-fasting plasma	GC-MS	AR C17:0/C21:0	NA	[30]

Table 4: Potential Biomarkers of Wheat Intake in Observation study

[2]containing more rye than control group

[3]This study was conducted in UK. WG wheat is the main WG source in British population. Considering this, although several types of WGs were used (WG wheat, corn, oats, barley and rice), WG wheat made up around 65% of the intervention

[4]This study was conducted in US. WG wheat is the dominant WG source in US populations.

[5]This cohort studies investigated

Searching results also showed some *Food compound intake biomarkers (FCIBs)* research as defined by Gao[19] such as phenolic compounds[31], benzoxazinoids[32] and phytoestrogen[33]. These compounds also present in other food, not specific for WG wheat. These results were summarized in Appendix.

Their concentrations varied in different cereal grains. Therefore, a combination of their metabolites could potentially indicate intake of different cereals.

4 Conclusions

Currently, there's no biomarkers reported for WG barley intake both in human and animal studies.

Total ARs and their metabolites were reported to potentially indicate WG wheat and rye intake. The homologues ratio of ARs C17:0/C21:0 was proposed to distinguish which whole grain type dominates in the diet.

Several phytochemicals could potential become candidate markers of WG wheat and barley intake. However, they need to be further validated.

5 Discussions

In order to clarify each sub-type of cereal's health beneficial effects, it is important to accurately quantify exposure amount of each sub-type. BFIs showed their strengths and potentials in studying WGs.

it is essential to discover intake biomarker for each sub-type cereal grain. Currently, most studies showed interest in WG effect biomarkers.

As discussed in [1], one of the challenges in BFIs discovery of WG is that the chemical compositions of most of WGs were not systematically

due to limited systematic research on phytochemicals

6 Appendix

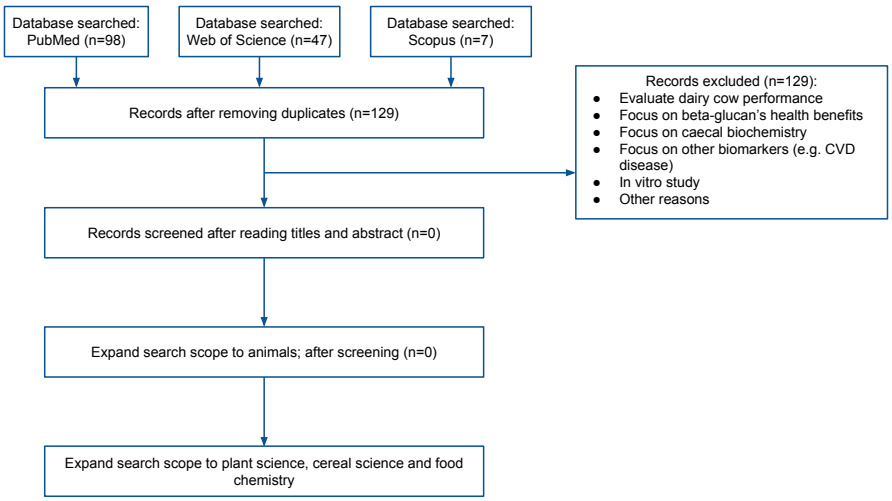

Figure 1: Flow chart of literature searching and screening for articles of barley intake biomarkers

Dietary factor	No. subjects	Study design	Sample type	Analytical method	Candidate biomarker(s)
Wheat bran, Wheat aleurone	14+13	randomized, cross-over, intervention	plasma	LC-MS/MS (Microbiology assay for folate)	betaine choline folate dimethylglycine (DMG)
None-bread, White bread, WG bread	155	observation[6]	urine	HPLC-qTOF-MS	Benzoxazinoid-related metabolites (HHPAA, HBOA glycoside) ARs-related metabolites(DHPPA glucuronide, DHPPTA sulphate), microbial

Table 5: Reported markers distinguishing WG wheat intake, but NOT specific

[6]dietary exposure measured from FFQ

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