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UNIVERSITY OF EASTERN FINLAND

Biomarkers for different types of cereals – Summary of the results from a recently published review article

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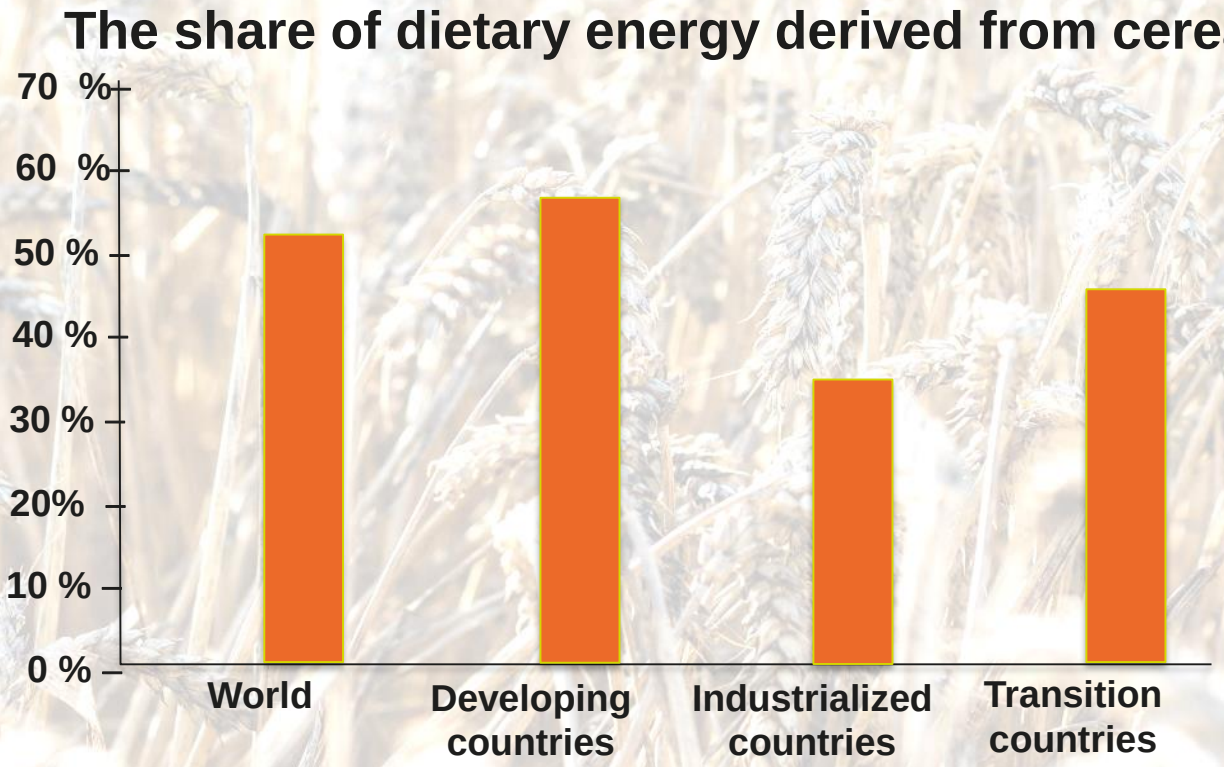
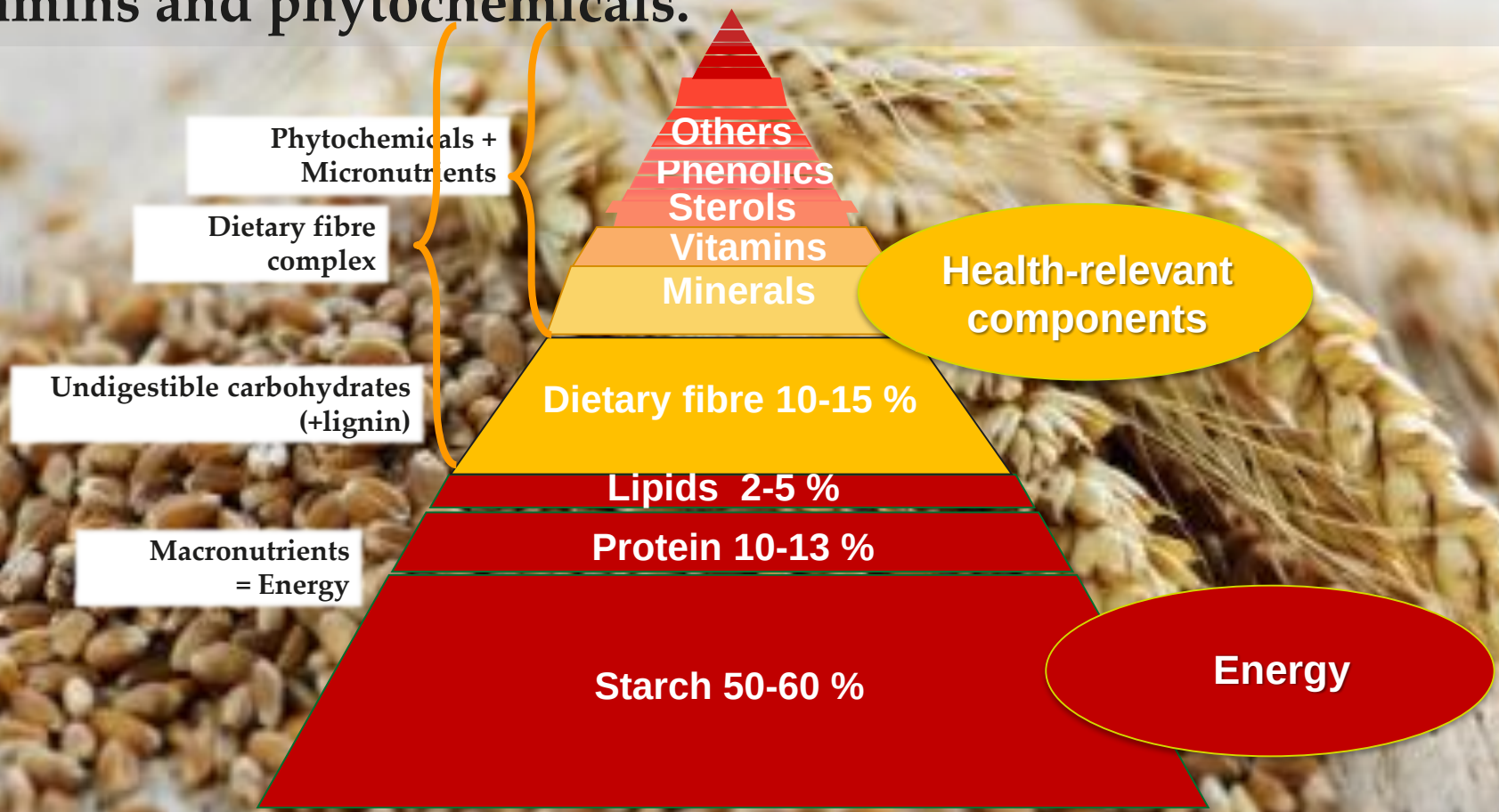
Grains are the most important contributor to the dietary energy intake globally.



Grains also are an important source of dietary fibre, minerals, vitamins and phytochemicals.



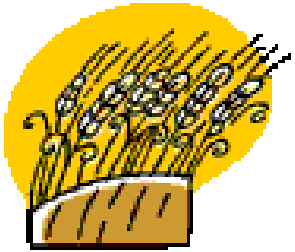
Oligo-Saccharides
Prebiotic

Phytate
Antioxidant

Dietary fibre
Improved glucose and lipid metabolism

Phytosterols
Cholesterol-lowering

Alkylrecorcinols
Enzyme inhibitors



Ferulic acid
Antioxidant

Lignans
Phytoestrogens

Tocopherols & -trienols
Antioxidants, reduce LDL oxidation

Vitamin E
antioxidant

Magnesium, chromium
Improved insulin sensitivity

Folate
Choline, betaine
Methyl donors

Synergistic effects

Beneficial physiological effects in humans

Health effects of whole grain

Observational evidence:

- Constantly associated with decreased risk for chronic non-communicable diseases
- Recent meta-analyses (Aune et al 2016, Aune et al 2013):
  - Decreased risk of coronary heart disease, cardiovascular disease, total cancer, all cause mortality, type 2 diabetes and obesity
- Scandinavian countries: whole grain bread
- United States: whole grain bread and breakfast cereals
- African countries: brown rice, unrefined maize and sorghum
- Asia: brown rice, although most of the rice consumed as white rice

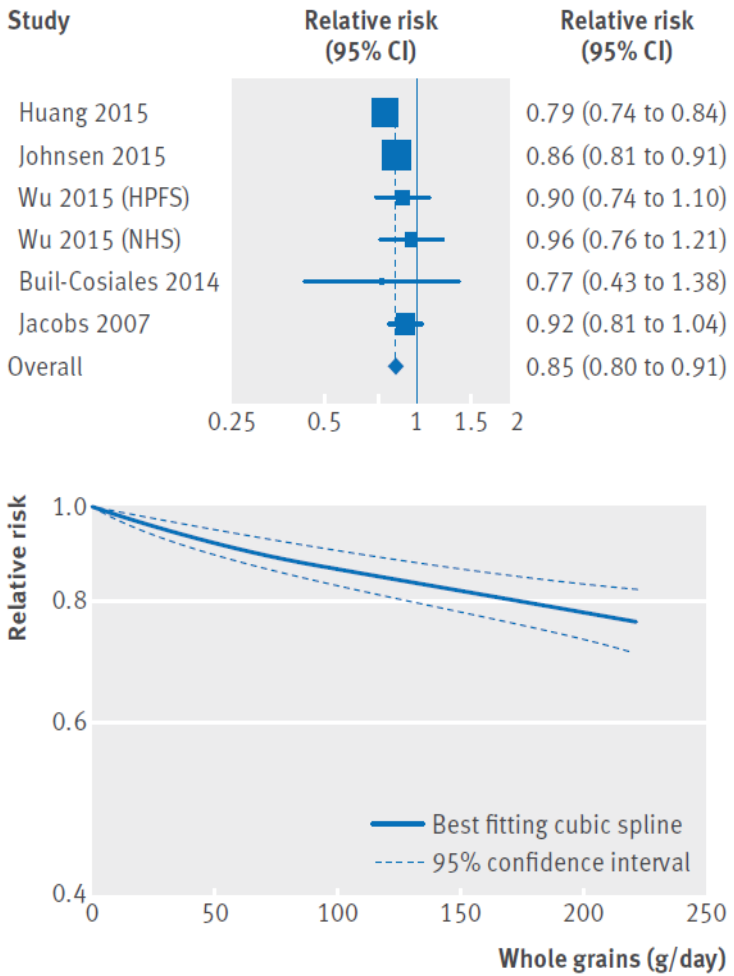


Fig 5 | Forest plot for consumption of whole grains (per 90 g/day) and risk of total cancer, with graph illustrating non-linear response

Clinical interventions/trials

- Outcomes on health benefits are less consistent
- Until today no dietary randomized intervention has been done investigating the effects of whole grain consumption on development on noncommunicable diseases:
  - Obvious reasons:
    - Too expensive
    - Decades of duration
- Indirect evidence from for example in Finnish Diabetes Prevention program:
  - Still after 15 year follow up those who belonged to intervention group for 4 years have decreased risk of Type 2 diabetes compared to those in control group
  - Whole grain and increased dietary fibre intake were among the key modification within the diet of intervention group

Nutrition, Metabolism & Cardiovascular Diseases (2014) **24**, 837–844

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

A whole-grain cereal-based diet lowers postprandial plasma insulin and triglyceride levels in individuals with metabolic syndrome☆

R. Giacco [a,*], G. Costabile [b], G. Della Pepa [b], G. Anniballi [b], E. Griffo [b], A. Mangione [b], P. Cipriano [b], D. Viscovo [b], G. Clemente [a], R. Landberg [c], G. Pacini [d], A.A. Rivellese [b], G. Riccardi [b]

PLOS ONE

RESEARCH ARTICLE

Effects of Unfermented and Fermented Whole Grain Rye Crisp Breads Served as Part of a Standardized Breakfast, on Appetite and Postprandial Glucose and Insulin Responses: A Randomized Cross-over Trial

Daniel P Johansson[1]*, Isabella Lee[1], Ulf Risérus[2], Maud Langton[1], Rikard Landberg[1,3]

CESS Freely available online

PLoS one

Whole grain wheat sourdough bread does not affect plasminogen activator inhibitor-1 in adults with normal or impaired carbohydrate metabolism☆,☆☆

K.A. MacKay, A.J. Tucker, A.M. Duncan, T.E. Graham, L.E. Robinson *

Whole Grain Products, Fish and Bilberries Alter Glucose and Lipid Metabolism in a Randomized, Controlled Trial: The Sysdimet Study

Maria Lankinen[1,2]*, Ursula Schwab[2,3], Marjukka Kolehmainen[4], Jussi Paananen[4], Kaisa Poutanen[4,5], Hannu Mykkänen[2], Tuulikki Seppänen-Laakso[5], Helena Gylling[2,3], Matti Uusitupa[2,6], Matej Orešič[5]

A whole-grain cereal-rich diet increases plasma betaine, and tends to decrease total and LDL-cholesterol compared with a refined-grain diet in healthy subjects

British Journal of Nutrition (2011), **105**, 1492–1502

Alastair B. Ross*, Stephen J. Bruce, Anny Blondel-Lubrano, Sylviane Oguey-Araymon, Maurice Beaumont, Alexandre Bourgeois, Corine Nielsen-Moennoz, Mario Vigo, Laurent-Bernard Fay, Sunil Kochhar, Rodrigo Bibiloni, Anne-Cécile Pittet, Shahram Emady-Azar, Dominik Grathwohl and Serge Rezzi

Gut microbiota

OPEN ACCESS

ORIGINAL ARTICLE

Whole grain-rich diet reduces body weight and systemic low-grade inflammation without inducing major changes of the gut microbiome: a randomised cross-over trial

Henrik Munch Roager,[1] Josef K Vogt,[2] Mette Kristensen,[3] Lea Benedicte S Hansen,[2] Sabine Ibrügger,[3] Rasmus B Mærkedahl,[3,4] Martin Iain Bahl,[1] Mads Vendelbo Lind,[3,5] Rikke L Nielsen,[2] Hanne Frøkiær,[4] Rikke Juul Gøbel,[6] Rikard Landberg,[5] Alastair B Ross,[5] Susanne Brix,[7] Jesper Holck,[8] Anne S Meyer,[8] Morten H Sparholt,[9] Anders F Christensen,[9] Vera Carvalho,[1] Bolette Hartmann,[6] Jens Juul Holst,[6,10] Jüri Johannes Rumessen,[11] Allan Linneberg,[12,13,14] Thomas Sicheritz-Pontén,[2] Marlene D Dalgaard,[7] Andreas Blennow,[15] Henrik Lauritz Frandsen,[1] Silas Villas-Bôas,[16] Karsten Kristiansen,[17] Henrik Vestergaard,[6,18] Torben Hansen,[6] Claus T Ekstrøm,[19] Christian Ritz,[3] Henrik Bjørn Nielsen,[2,20] Oluf Borbye Pedersen,[6] Ramneek Gupta,[2] Lotte Lauritzen,[3] Tine Rask Licht[1]

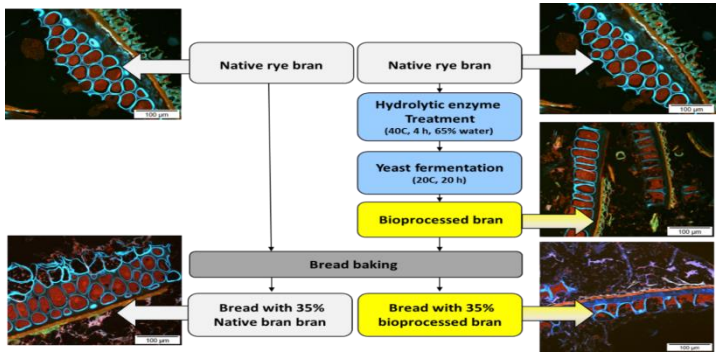
Dietary carbohydrate modification enhances insulin secretion persons with the metabolic syndrome[1–3]

David E Laaksonen, Leena K Toppinen, Katri S Juntunen, Karin Autio, Kirsi-Helena Liukkonen, Kaisa S P[illegible] Leo Niskanen, and Hannu M Mykkänen

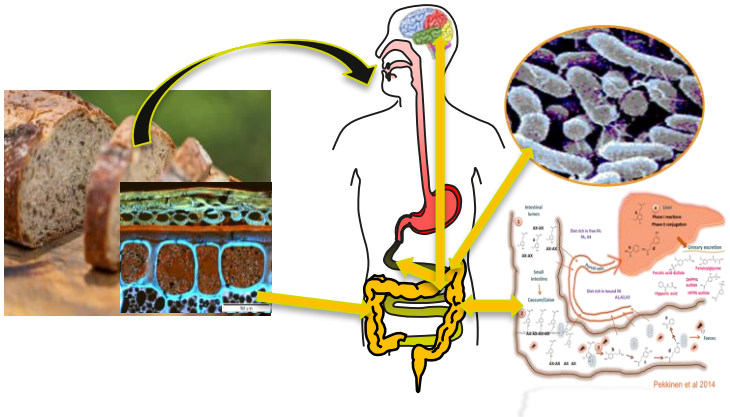
Am J Clin Nutr 2005;82:1218–27.

Factors contributing the health benefits of whole grain

- Rich in dietary fiber, vitamins, minerals, unsaturated fatty acids, phytochemicals
- Structure of the cereal foods may
  - encapsulate nutrients → slow digestion and absorption → causal for health benefits
- Non-digestibles interact with colonic microbiota, modulating its activity and delivering metabolites
  - Specific dietary fibers in cereal foods, such as β-glucans, the fructans, and resistant starches
- Food structures may have an effect on the regulation of eating
- Others….

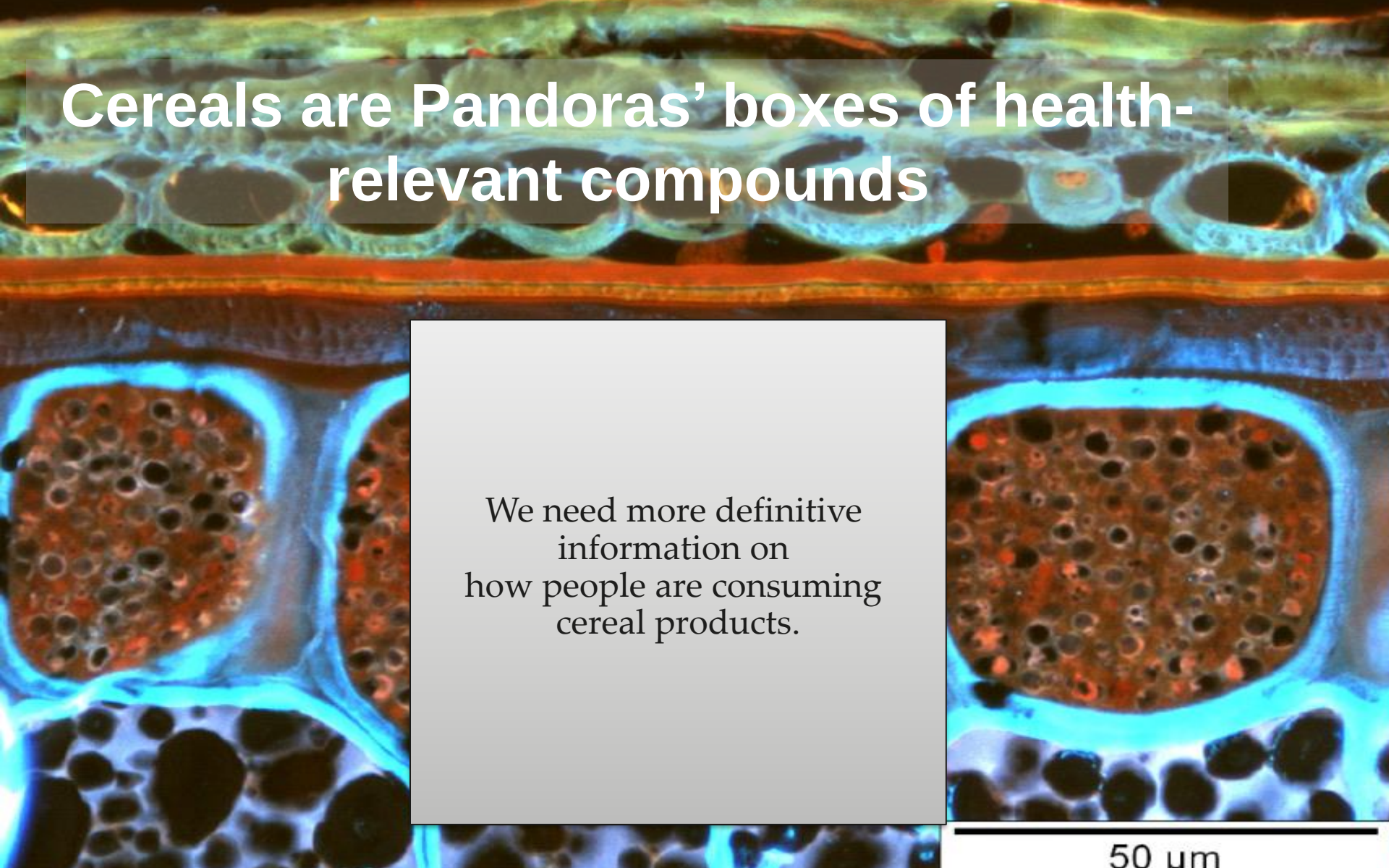


(protein: red; beta-glucan rich cell walls: light blue)



Cereals are Pandoras' boxes of health-relevant compounds

We need more definitive information on how people are consuming cereal products.



Challenges of reporting cereal intake

- Whole grain intake is associated with an overall healthy lifestyle and dietary pattern
  - to study the independent impact of whole grains per se on health outcomes is difficult, despite adjustment for confounding factors
- Methods for studying the dietary intake lack the precision for accurately measure the intake of different grains separately
- Habitual whole grain intake with common self-reporting techniques may cause difficulties for consumers to distinguish or identify different grains and to understand portion sizes
- Subjective methodology is affected by under- and over reporting
- Whole-grain products have a large variation in whole-grain content
- There is no uniform definition of whole-grain products or serving size to be applied across studies
  - attenuate the association between whole grain and disease towards null
  - preventing discovery of existing associations

Why would we need biomarkers of cereal consumption?

- Using dietary biomarkers that reflect the intake of specific whole grains, grain fractions, and refined grains could be a strategy
  - to improve whole-grain intake ranking in observational studies
  - to address compliance in dietary intervention studies
  - to be combined with traditional methods to improve the accuracy of intake estimations
- Only a few dietary biomarkers that reflect specific wholegrain intakes have been suggested
- No biomarkers of refined grains have been described

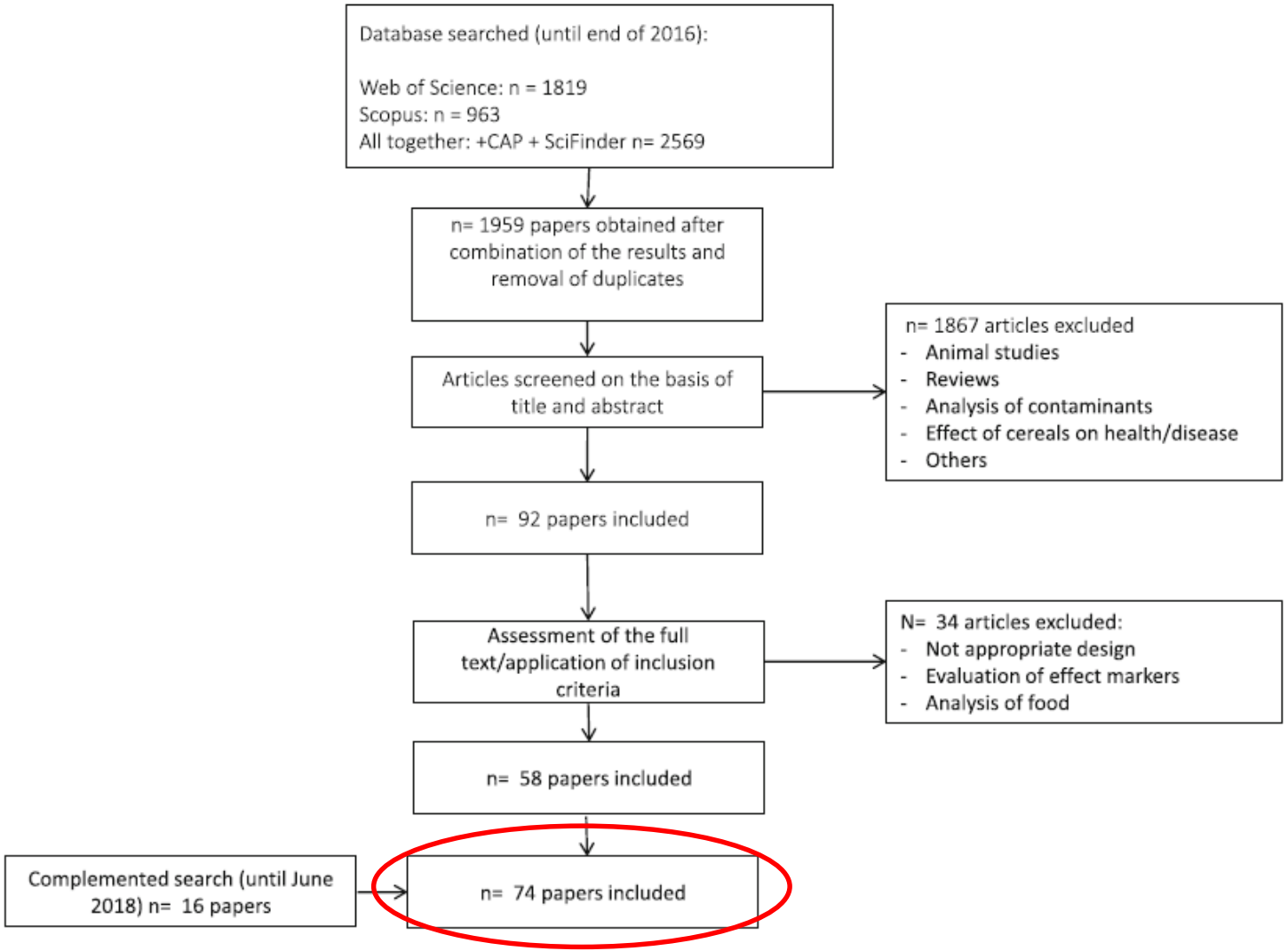
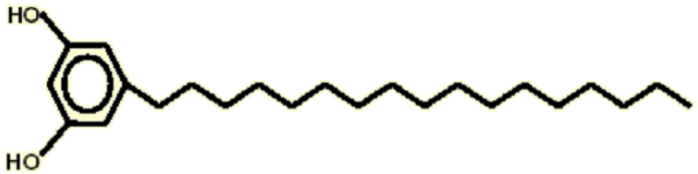


Fig. 1 Flow diagram of study selection

Potential biomarkers of cereal intake

Alkylresorcinols

- Phenolic lipids, specific biomarkers for whole grain wheat and rye intake, small amounts on barley
- Is located in bran → indicate the consumption of the whole grain versions
- Several studies done indicating their specificity for rye and wheat independently of food matrix
- **Ratio of C17:0 to C21:0 homologues in plasma is approximately 1.0 in rye, 0.1 in wheat and 0.001 in durum wheat**
- Short half life in plasma → long term stable and frequent intake of rye and/or wheat
  - Not suitable for populations with low or occational consumption
- Urinary excretion of metabolites, DHBA, DHPPA, DHPPTA and DHCA have similar validity as plasma AR concentrations in free-living subjects with high and frequent intake
  - Not suitable for urine spot sampling at the moment



Associated for example with increased insulin sensitivity and improved lipid profile in Nordic healthy diet as well as having antioxidant and anticancer activity.

Benzoxazinoids

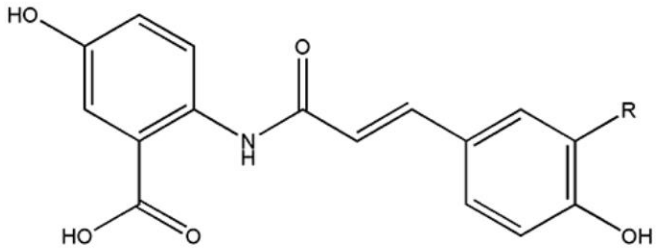
- Specific derivatives almost exclusively found in wheat and rye grains
- Highest amounts of benzoxazinoid compounds:
  - Flour: fine-rye flour (3.6 mg/g dry weight)
  - Bread products: Finnish rye breads (2.3–3.3 mg/ g dry weight)
- Double-hexose conjugated 2,4-dihydroxy-1,4-benzoxazin-3-one (DIBOA) the main benzoxazinoid metabolite
- Concentration is largely effected by technological processing in foods
  - Sourdough fermentation may degrade
- Concentration in plasma, urine and tissues is largely effected by endogenous metabolism and microbiota fermentation
  - Increased plasma, urine, and tissue benzoxazinoid concentrations after intake of benzoxazinoid-rich foods from wheat and rye, but large fluctuations in long term effects apparent
- More studies needed to evaluate the feasibility of individual benzoxazinoids and their metabolites as biomarkers of WG intake

2,4-dihydroxy-1,4-benzoxazin-3-one, **DIBOA**

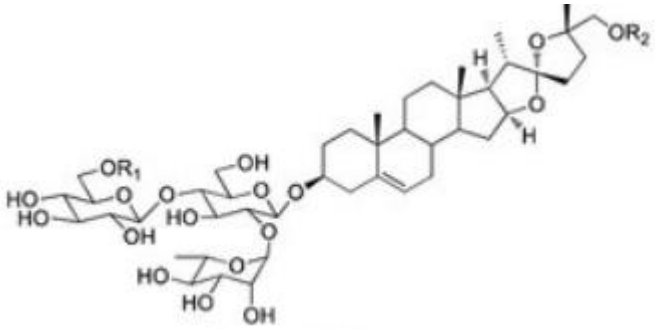
Wide range of biological properties including antimicrobial, antifeedant, and insecticidal effects.

Biomarkers of whole-grain oat intake

- Oats contains two classes of unique compounds: avenanthramides and steroidal saponins, i.e. avenacosides
- Avenanthramides show low bioavailability in humans
  - Half lifes 2-5 h in serum, up to 8 hours in urine
  - Some metabolites may have longer half lifes and may thus reflect better the intake – but not all volunteers produce these metabolites
- Avenacosides A and B (AVE-A and –B)
  - metabolic fate of AVEs has been investigated in only one study: urine concentrations during 48 h after a single dose of oat bran (n=12)
  - Rapid increase in concentrations of AVE-A and -B half lives being 4-6 hours
  - Evident effect of gut microbiota fermentation
- Potential as short-to-medium-term biomarkers of oat intake, since they are unique for
- Low bioavailability and rapid metabolism affects their potential and thus, validation studies are needed to confirm biomarker status



Avenanthramide

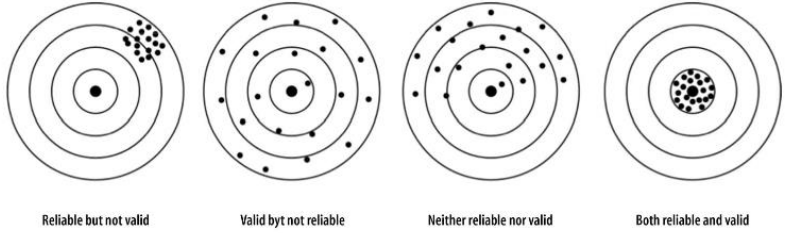


Avenacoside A

Biomarkers of quinoa and rice intake

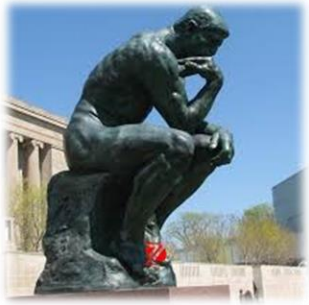
- Quinoa:
  - 30 alkylresorcinol derivatives including odd-, even-, branched-chain and methyl-alkylresorcinols
  - similar magnitude as those quantified in barley
  - unique alkylresorcinol homolog composition profile with even-numbered alkylresorcinol homologs
    - C18:0, C20:0, C22:0, and C24:0 concentrations increased after quinoa consumption
  - feasible as biomarkers of quinoa intake
  - Validation studies needed to assess halflife, dose response, reproducibility, and validity under controlled intake and under free-living conditions
- Rice:
  - Rice bran metabolites detected in plasma: methionine sulfone, alpha-hydroxycaproate, linoleoyllinolenoyl-glycerol, palmitoyl-linolenoylglycerol, pyridoxal, 2-hydroxyhippurate, salicylate, gammaglutamylglutamate, gamma-glutamylthreonine, hypoxanthine, and dihydroorotate… (plasma and feaces)
  - It is still unclear if they would specifically reflect rice bran intake
  - Many phenolic compounds suggested to be used as biomarkers, but may be too unspecific

Biomarker validity and reproducibility —key features of biomarkers



- Validity
  - Lack of systematic measurement error when comparing the actual observation with that obtained, reference method needed
  - Biomarker specificity for a specific food, its pharmacokinetics, dose-response, and its non-dietary determinants
  - Estimation of the validity under different conditions in different populations
- Reproducibility
  - correlation between samplings within the same individual on independent occasions
  - largely determined by the stability of the individual's intake of the food/nutrient of interest and the elimination half-life of the biomarker
- Most food biomarkers are concentration biomarkers - accuracy varies and is dependent on:
  - differences in bioavailability of the biomarker substance within and between subjects, differences in metabolism, interactions with other dietary components, differences in distribution volume among subjects and the impact of gut microbiota

Conclusions



- Several biomarker candidates for whole-grain wheat, rye, and oats have been discovered
- Uniquely found in biological samples from humans after consumption and can be traced down to actual compounds in the food
- Validity and reliability typically remains to be evaluated under controlled and free-living conditions in humans
- Within and between individual variability needs to be studied further
- Alkylresorcinols and their metabolites are rare examples of food biomarkers that have been extensively validated as biomarkers of whole-grain wheat and rye intake in various matrixes

FOODBALL
The Food Biomarker Alliance

Thank you!

Xiaofei Yin

Izabela Biskup

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Landberg *et al. Genes & Nutrition* (2019) 14:28
https://doi.org/10.1186/s12263-019-0651-9

Genes & Nutrition

REVIEW Open Access

Biomarkers of cereal food intake

Rikard Landberg[1*], Kati Hanhineva[2], Kieran Tuohy[3], Mar Garcia-Aloy[4,5], Izabela Biskup[1], Rafael Llorach[4,5], Xiaofei Yin[6], Lorraine Brennan[6] and Marjukka Kolehmainen[2]