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Composition of pork and German meat products with a focus on iron, selenium and iodine.
Schöne F, Ibel A, Lorkowski S, Ihling M, Ramminger S, Kirmse R, Spörl K, Kießling G, Glei M.
Journal of Food Composition and Analysis 119 **(**2023**)** 105246

Meat products contribute to the fat and salt burden of German consumers, however, they represent also a valuable source of protein, iron, selenium and further micronutrients. An assortment of ten representative meat products – from 15 processors - was to be compared with lean (muscle) pork. The meat products differed significantly in their content of water, fat, protein and salt, resulting in respective changes to the content of Ca, K, Mg, P, Cu, Mn, Se and Zn. Meat and meat products were confirmed as relevant source of Se (medians 64–156 µg/ kg) and Fe (5–86 mg/kg). The maxima represent liver and blood sausage, the minima Jagdwurst and smoked belly. Ten processors used non-iodized salt resulting in low-iodine meat products - median 32 µg/kg and not far from pork (4 µg iodine/kg). Iodized salt (15–25 µg/g iodine) was used by five processors, that transformed meat products into iodine sources (medians 347–671 µg/kg). The high-significant regression between the iodine and NaCl concentrations for all meat products with iodized salt allows to calculate the food-iodine content from the salt dosage. As regards Fe, Se and iodine, the food tables for pork and meat products should be updated, including for cases where iodized salt is used.

Potential Role of ROS in Butyrate- and Dietary Fiber-Mediated Growth Inhibition and Modulation of Cell Cycle-, Apoptosis- and Antioxidant-Relevant Proteins in LT97 Colon Adenoma and HT29 Colon Carcinoma Cells.
Schlörmann W, Horlebein C, Hübner SM, Wittwer E, Glei M.
Cancers (Basel). 2023 Jan 10;15(2):440. doi: 10.3390/cancers15020440.

The aim of the present study was to examine whether reactive oxygen species (ROS) contribute to chemopreventive effects of fermentation supernatants (FS) of different dietary fibers (Synergy1®, oat-, barley-, yeast β-glucan, Curdlan) and butyrate as a fermentation metabolite. LT97 and HT29 cells were treated with butyrate and FS alone or with *N*-acetyl-cysteine (NAC) and their impact on ROS formation, cell growth, and protein expression (Cyclin D2, p21, PARP, Bid, GPx2) was investigated. Butyrate and FS significantly decreased cell growth. ROS levels were significantly increased, particularly in LT97 cells, while co-treatment with NAC decreased ROS formation and growth inhibitory effects in both cell lines. After treatment with butyrate and FS, Cyclin D2 expression was reduced in LT97 cells and p21 expression was increased in both cell lines. Levels of full-length PARP and Bid were decreased, while levels of cleaved PARP were enhanced. GPx2 expression was significantly reduced by fiber FS in HT29 cells. A notable effect of NAC on butyrate- and FS-modulated protein expression was observed exclusively for PARP and Bid in HT29 cells. From the present results, a contribution of ROS to growth inhibitory and apoptotic effects of butyrate and FS on LT97 and HT29 cells cannot be excluded.

Lehrbuch „Nutrigenomik – Gene und unsere Ernährung“
Carlberg C, Klotz LO, Molnar F.
Springer-Verlag, https://doi.org/10.1007/978-3-662-65342-5

Effect of a regular consumption of traditional and roasted oat and barley flakes on blood lipids and glucose metabolism-A randomized crossover trial.
Reiners S, Hebestreit S, Wedekind L, Kiehntopf M, Klink A, Rummler S, Glei M, Lorkowski S, Schlörmann W, Dawczynski C.
Front Nutr. 2023 Feb 2;10:1095245. doi: 10.3389/fnut.2023.1095245. eCollection 2023.

Background: Regular consumption of the soluble dietary fiber β-glucan is associated with decreased total cholesterol (TC), low-density lipoprotein (LDL) cholesterol and blood glucose. Barley and oat flakes as natural sources of β-glucan were roasted to improve sensory quality. The aim of this study was to investigate whether roasting of barley and oat flakes changes the physiological impact of the β-glucan-rich flakes on glucose and lipid metabolism. **Method:** A five-armed randomized crossover trial design was used. The intervention study was conducted from May 2018 to May 2019 and included 32 healthy subjects with moderately increased LDL cholesterol (≥2.5 mmol/L). During the 3-week intervention periods, 80 g of roasted or traditional barley or oat flakes, or four slices of white toast bread per day were consumed for breakfast. At the start and the end of each intervention, fasting and postprandial blood was taken. The intervention periods were separated by 3-week wash-out periods. **Results:** During the interventions with the cereal flakes, TC and LDL cholesterol concentrations were significantly reduced compared to baseline values by mean differences of 0.27-0.33 mmol/L and 0.21-0.30 mmol/L, respectively ($p < 0.05$), while high-density lipoprotein (HDL) cholesterol was only reduced after the intervention with barley flakes ($p < 0.05$). After the intervention period with toast, TC and HDL cholesterol increased ($p < 0.05$). The fasting levels of triglycerides, fasting blood glucose and insulin did not change in any group. The effects of traditional and roasted varieties on blood lipids did not differ between the groups. **Conclusion:** The regular consumption of traditional or roasted barley and oat flakes contributes to the management of cardiovascular diseases by improving TC and LDL cholesterol.

Patientenflyer: Ernährung und Psychische Gesundheit.
Dawczynski C, Kolassa I. Flyer 2023. DOI: 10.22032/dbt.53463

Impact of Regular Intake of Microalgae on Nutrient Supply and Cardiovascular Risk Factors: Results from the NovAL Intervention Study.
Sandgruber F, Höger A-L, Kunze J, Schenz B, Griehl C, Kiehntopf M, Kipp K, Kühn J, Stangl GI, Lorkowski S, Dawczynski C. Nutrients 2023, 15(7), 1645. https://doi.org/10.3390/nu15071645

A 14-day randomized controlled study with a parallel design was conducted with 80 healthy participants. Intervention groups I (IG1) and II (IG2) received a defined background diet and consumed a smoothie enriched with either 15 g of Chlorella dry weight (d.w.) or 15 g of Microchloropsis d.w. daily. Control group II (CG2) received a defined background diet without the smoothie. Control group I (CG1) received neither. Blood samples and 24-h urine were collected at the beginning and the end of the study. Serum concentrations of 25-hydroxyvitamin D3, vitamin D3, selenium, iron, ferritin, transferrin saturation, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, non-HDL cholesterol and the LDL-cholesterol/HDL cholesterol ratio decreased in IG1 ($p < 0.05$), while 25-hydroxyvitamin D2 increased ($p < 0.05$). In IG2, vitamin D3, 25-hydroxyvitamins D2 and D3 decreased ($p < 0.05$), while concentrations of fatty acids C20:5n3 and C22:5n3 increased. Serum and urine uric acid increased in IG1 and IG2 ($p < 0.05$). Microchloropsis is a valuable source of n3 fatty acids, as is Chlorella of vitamin D2. Regular consumption of Chlorella may affect the iron and selenium status negatively but may impact blood lipids positively. An elevated uric acid concentration in blood and urine following the regular consumption of microalgae poses potential risks for human health.

Role of Dietary Fiber and Energy Intake on Gut Microbiome in Vegans, Vegetarians, and Flexitarians in Comparison to Omnivores—Insights from the Nutritional Evaluation (NuEva) Study.
Seel W, Reiners S, Kipp K, Simon M-C, Dawczynski C. Nutrients 2023, 15, 1914. https://doi.org/10.3390/nu15081914

In recent years, there has been a global trend towards a plant-based lifestyle. In the NuEva study, dietary self-reports of 258 participants following one of four diets (Western diet (WD), flexitarians (Flex), vegetarians (VG), and vegans (VN)) were related to fecal microbiome composition. Reduced consumption of animal products (VN < VG < Flex < WD) was associated with a decreased intake of energy ($p < 0.05$), and an increased intake of soluble and non-soluble dietary fibers ($p < 0.05$). We observed the lowest average microbiome diversity in vegans and the highest in WD. Compared to WD, VG ($p < 0.05$) and VN ($p < 0.01$) differed significantly in their bacterial composition. These data were related to dietary fiber intake. Furthermore, we identified 14 diet-specific biomarkers at the genus level by using LefSe analysis. Of these, 11 showed minimum or maximum counts in WD or VN. While the VN-specific species were inversely associated with cardiovascular risk factors, a positive association was detected for the WD-specific species. Identifying biomarkers for the diets on extreme ends of the spectrum (WD and VN) and their association with cardiovascular risk factors provides a solid evidence base highlighting the potential and the need for the development of personalized recommendations dependent on dietary patterns. Even so, the mechanisms underlying these diet-specific differences in microbiome composition cannot yet be clearly assessed. The elucidation of these associations will provide the basis for personalized nutritional recommendations based on the microbiome.

Effects of Histamine and the α-Tocopherol Metabolite α-13'-COOH in an Atopic Dermatitis Full-Thickness Skin Model

Riedl R, Wallert M, Lorkowski S, Wiegand C.

Molecules. 2023 Jan 3;28(1):440. doi: 10.3390/molecules28010440.

Atopic dermatitis is a T-cell mediated inflammatory skin disease with detected elevated levels of histamine in skin or plasma. In this study, the effects of histamine in a TH2 cytokine environment on human keratinocytes and three-dimensional skin models were investigated. These models were used to explore the anti-inflammatory properties of the α-tocopherol-derived long-chain metabolite α-13'-carboxychromanol (α-13'-COOH). Histamine and TH2 cytokine-induced proliferation of keratinocytes was studied using a scratch assay. The inflammatory marker interleukin-8 was significantly increased in healthy and TH2 cytokine-stimulated keratinocytes and skin models after histamine treatment. The incubation of full-thickness skin models with TH2 cytokines and histamine resulted in morphological changes in the epidermal layer, interpreted as hyperkeratosis. α-13'-COOH significantly decreased interleukin-8 in these disease-associated skin models. Histological staining of filaggrin showed skin-strengthening effects following α-13'-COOH treatment, without changes in mRNA expression. Cytokeratin 10 mRNA expression tended to be increased in response to α-13'-COOH. Anti-allergic properties of α-13'-COOH were studied by pre-incubation of human leukocytes with α-13'-COOH. This resulted in reduced sulfido-leukotriene synthesis. The hyperproliferation effect of histamine in atopic dermatitis skin models may be of further interest to the study of disease-associated morphological changes. Moreover, α-13'-COOH is a promising natural compound for the treatment of inflammatory skin diseases.

Requirement of transcription-coupled nucleotide excision repair for the removal of a specific type of oxidatively induced DNA damage.

Sarmini L, Meabed M, Emmanouil E, Atsaves G, Robeska E, Karwowski BT, Campalans A, Gimisis T, Khobta A.

Nucleic Acids Research, 2023 Apr 7 (online ahead of print): gkad256. doi: 10.1093/nar/gkad256

Accumulation of DNA damage resulting from reactive oxygen species was proposed to cause neurological and degenerative disease in patients, deficient in nucleotide excision repair (NER) or its transcription-coupled subpathway (TC-NER). Here, we assessed the requirement of TC-NER for the repair of specific types of oxidatively generated DNA modifications. We incorporated synthetic 5',8-cyclo-2'-deoxypurine nucleotides (cyclo-dA, cyclo-dG) and thymine glycol (Tg) into an EGFP reporter gene to measure transcription-blocking potentials of these modifications in human cells. Using null mutants, we further identified the relevant DNA repair components by a host cell reactivation approach. The results indicated that NTHL1-initiated base excision repair is by far the most efficient pathway for Tg. Moreover, Tg was efficiently bypassed during transcription, which effectively rules out TC-NER as an alternative repair mechanism. In a sharp contrast, both cyclopurine lesions robustly blocked transcription and were repaired by NER, wherein the specific TC-NER components CSB/ERCC6 and CSA/ERCC8 were as essential as XPA. Instead, repair of classical NER substrates, cyclobutane pyrimidine dimer and N-(deoxyguanosin-8-yl)-2-acetylaminofluorene, occurred even when TC-NER was disrupted. The strict requirement of TC-NER highlights cyclo-dA and cyclo-dG as candidate damage types, accountable for cytotoxic and degenerative responses in individuals affected by genetic defects in this pathway.

Patient-reported experiences with side effects of kidney cancer therapies and corresponding information flow.

Kastrati K, Mathies V, Kipp AP, Huebner J.

J Patient Rep Outcomes. 2022 Dec 16;6(1):126. doi: 10.1186/s41687-022-00533-z.

Background: Treatment options for metastatic renal cell carcinoma (mRCC) have improved over recent years. Various therapies for metastatic renal cell carcinoma are currently approved for first and successive lines. Having various treatment options makes it important to reflect how patients experience side effects in the real-world setting. So far, data on the side effects of these treatments have only been collected within clinical trials, and have been mostly assessed by the investigator and not as patient-reported outcomes. Our aim was to determine patient-reported experiences of side effects in the real-world setting and to evaluate the doctor-patient communication regarding side effects. Data were collected via an anonymous, voluntary online survey given to members of a support group for RCC; the questionnaire was completed by 104 mRCC patients.

Results: 89.1% of participants were suffering from side effects of any grade. These appeared to be higher for patients treated with tyrosine kinase inhibitors compared to those treated with immune-checkpoint inhibitors (98.4% vs. 68.4%). However, information on side effects is scarce: 4.0% had never heard anything about them while only 18.8% of participants received detailed information on possible side effects. Although 85.6% of participants reported side effects to their physician, 34.6% did not encounter an improvement. Limitations of the study include the design as an online questionnaire and the small sample, consisting only of members of a support group.

Conclusions: Differences can be seen between patient-reported side effects within our survey and those based on clinical trials. A shift towards more patient-reported outcomes is needed. In addition, patients seeking the advice of their physician on side effects are in need of more-or better-information and support.

Ferroptosis-modulating small molecules for targeting drug-resistant cancer: Challenges and opportunities in manipulating redox signaling.
Koeberle SC, Kipp AP, Stuppner H, Koeberle A.
Med Res Rev. 2023 May;43(3):614-682. doi: 10.1002/med.21933. Epub 2023 Jan 19.

Ferroptosis is an iron-dependent cell death program that is characterized by excessive lipid peroxidation. Triggering ferroptosis has been proposed as a promising strategy to fight cancer and overcome drug resistance in antitumor therapy. Understanding the molecular interactions and structural features of ferroptosis-inducing compounds might therefore open the door to efficient pharmacological strategies against aggressive, metastatic, and therapy-resistant cancer. We here summarize the molecular mechanisms and structural requirements of ferroptosis-inducing small molecules that target central players in ferroptosis. Focus is placed on (i) glutathione peroxidase (GPX) 4, the only GPX isoenzyme that detoxifies complex membrane-bound lipid hydroperoxides, (ii) the cystine/glutamate antiporter system Xc - that is central for glutathione regeneration, (iii) the redox-protective transcription factor nuclear factor erythroid 2-related factor (NRF2), and (iv) GPX4 repression in combination with induced heme degradation via heme oxygenase-1. We deduce common features for efficient ferroptotic activity and highlight challenges in drug development. Moreover, we critically discuss the potential of natural products as ferroptosis-inducing lead structures and provide a comprehensive overview of structurally diverse biogenic and bioinspired small molecules that trigger ferroptosis via iron oxidation, inhibition of the thioredoxin/thioredoxin reductase system or less defined modes of action.

Measurement of trace elements in murine liver tissue samples: Comparison between ICP-MS/MS and TXRF.
Lossow K, Schlörmann W, Tuchtenhagen M, Schwarz M, Schwerdtle T, Kipp AP.
J Trace Elem Med Biol. 2023 Mar 30;78:127167. doi: 10.1016/j.jtemb.2023.127167. Online ahead of print.

Background: Trace elements exhibit essential functions in many physiological processes. Thus, for research focusing on trace element homeostasis and metabolism analytical methods allowing for multi-element analyses are fundamental. Small sample amounts may be a big challenge in trace element analyses especially if also other end points want to be addressed in the same sample. Therefore, the aim of the present study was to examine trace elements (iron, copper, zinc, and selenium) in murine liver tissue prepared by a RIPA buffer-based lyses method. Methods and results: After centrifugation, lysates and pellets were obtained and trace elements were analyzed with TXRF in liver lysates. The results were compared to that obtained by a standard microwave-assisted acidic digestion with subsequent ICP-MS/MS analysis of the same liver tissue, liver lysates, and remaining pellets. In addition, trace element concentrations, determined in murine serum with both methods, were compared. For serum samples, both TXRF and ICP-MS/MS provide similar and highly correlating results. Furthermore, in liver lysate samples prepared with RIPA buffer, comparable trace element concentrations were measured by TXRF as with the standard digestion technique and ICP-MS/MS. Only marginal amounts of trace elements were detected in the pellets.
Conclusion: Taken together, the results obtained by the present study indicate that the RIPA buffer-based method is suitable for sample preparation for trace element analyses via TXRF, at least for the here investigated murine liver samples.

Side-by-side comparison of recombinant human glutathione peroxidases identifies overlapping substrate specificities for soluble hydroperoxides.

Schwarz M, Löser A, Cheng Q, Wichmann-Costaganna M, Schädel P, Werz O, Arnér ES, Kipp AP.

Redox Biol. 2023 Feb;59:102593. doi: 10.1016/j.redox.2022.102593. Epub 2023 Jan 2.

Five out of eight human glutathione peroxidases (GPXs) are selenoproteins, representing proteins that contain selenium as part of the amino acid selenocysteine. The GPXs are important for reducing hydroperoxides in a glutathione-consuming manner and thus regulate cellular redox homeostasis. GPX1, GPX2, and GPX4 represent the three main cytosolic GPXs, but they differ in their expression patterns with GPX1 and GPX4 being expressed ubiquitously, whereas GPX2 is mainly expressed in epithelial cells. GPX1 and GPX2 have been described to reduce soluble hydroperoxides, while GPX4 reduces complex lipid hydroperoxides, thus protecting cells from lipid peroxidation and ferroptosis. But most of these data are derived from cells that are devoid of one of the isoforms and thus, compensation or other cellular effects might affect the conclusions. So far, the use of isolated recombinant human selenoprotein glutathione peroxidases in pure enzyme assays has not been employed to study their substrate specificities side by side. Using recombinant GPX1, GPX2, and GPX4 produced in E. coli we here assessed their GPX activities by a NADPH-consuming glutathione reductase-coupled assay with 17 different peroxides (all at 50 μM) as substrates. GPX4 was clearly the only isoform able to reduce phosphatidylcholine hydroperoxide. In contrast, small soluble hydroperoxides such as H2O2, cumene hydroperoxide, and tert-butyl hydroperoxide were reduced by all three isoforms, but with approximately 10-fold higher efficiency for GPX1 in comparison to GPX2 and GPX4. Also, several fatty acid-derived hydroperoxides were reduced by all three isoforms and again GPX1 had the highest activity. Interestingly, the stereoisomerism of the fatty acid-derived hydroperoxides clearly affected the activity of the GPX enzymes. Overall, distinct substrate specificity is obvious for GPX4, but not so when comparing GPX1 and GPX2. Clearly GPX1 was the most potent isoform of the three GPXs in terms of turnover in reduction of soluble and fatty-acid derived hydroperoxides.

Selenium homeostasis in human brain cells: Effects of copper (II) and Se species.

Raschke S, Ebert F, Kipp AP, Kopp JF, Schwerdtle T.

J Trace Elem Med Biol. 2023 Mar 12;78:127149. doi: 10.1016/j.jtemb.2023.127149. Online ahead of print.

Background: Both essential trace elements selenium (Se) and copper (Cu) play an important role in maintaining brain function. Homeostasis of Cu, which is tightly regulated under physiological conditions, seems to be disturbed in Alzheimer´s (AD) and Parkinson´s disease (PD) patients. Excess Cu promotes the formation of oxidative stress, which is thought to be a major cause for development and progression of neurological diseases (NDs). Most selenoproteins exhibit antioxidative properties and may counteract oxidative stress. However, expression of selenoproteins is altered under conditions of Se deficiency. Serum Se levels are decreased in AD and PD patients suggesting Se as an important factor in the development and progression of NDs. The aim of this study was to elucidate the interactions between Cu and Se in human brain cells particularly with respect to Se homeostasis.
Methods: Firstly, modulation of Se status by selenite or SeMet were assessed in human astrocytes and human differentiated neurons. Therefore, cellular total Se content, intra- and extracellular selenoprotein P (SELENOP) content, and glutathione peroxidase (GPX) activity were quantified. Secondly, to investigate the impact of Cu on these markers, cells were exposed to copper(II)sulphate ($CuSO_4$) for 48 h. In addition, putative protective effects of Se on Cu-induced toxicity, as measured by cell viability, DNA damage, and neurodegeneration were investigated.
Results: Modulation of cellular Se status was strongly dependent on Se species. In detail, SeMet increased total cellular Se and SELENOP content, whereas selenite led to increased GPX activity and SELENOP excretion. Cu treatment resulted in 133-fold higher cellular Cu concentration with a concomitant decrease in Se content. Additionally, SELENOP excretion was suppressed in both cell lines, while GPX activity was diminished only in astrocytes. These effects of Cu could be partially prevented by the addition of Se depending on the cell line and Se species used. While Cu-induced oxidative DNA damage could not be prevented by addition of Se regardless of chemical species, SeMet protected against neurite network degeneration triggered by Cu.
Conclusion: Cu appears to negatively affect Se status in astrocytes and neurons. Especially with regard to an altered homeostasis of those trace elements during aging, this interaction is of high physiological relevance. Increasing Cu concentrations associated with decreased selenoprotein expression or functionality might be a promoting factor for the development of NDs.