1. Folic acid supplements during pregnancy and child psychomotor development after the first year of life.

JAMA Pediatr. 2014 Nov;168(11):e142611. doi: 10.1001/jamapediatrics.2014.2611. Epub 2014 Nov 3.

Valera-Gran D, García de la Hera M, Navarrete-Muñoz EM, Fernandez-Somoano A, Tardón A, Julvez J, Forns J, Lertxundi N, Ibarluzea JM, Murcia M, Rebagliato M, Vioque J.

Abstract:
IMPORTANCE: Folate intake during pregnancy has been associated with improved neuropsychological development in children, although the effects of high dosages of folic acid (FA) supplements are unclear. OBJECTIVE: To examine the association between the use of high dosages of FA supplements during pregnancy and child neuropsychological development after the first year of life. DESIGN, SETTING, AND PATIENTS: The multicenter prospective mother-child cohort Infancia y Medio Ambiente (INMA) Project recruited pregnant women from 4 areas of Spain (Asturias, Sabadell, Gipuzkoa, and Valencia) between November 2003 and January 2008. Pregnant women completed an interviewer-administered questionnaire on the usual dietary folate intake and FA supplements at 10 to 13 weeks and 28 to 32 weeks of gestation. The main analyses were based on a sample of 2213 children with complete information on neuropsychological development and FA supplement intake during pregnancy. Multiple linear and logistic regression analyses were used to explore the effects of FA supplements on child neuropsychological development. MAIN OUTCOMES AND MEASURES: Neuropsychological development was assessed using the Bayley Scales of Infant Development. We calculated mental scale and psychomotor scale scores. One SD below the mean established a delay in neurodevelopment (score <85). RESULTS: A high proportion of women (57.3%) did not reach the recommended dosages of FA supplements (400 μg/d), but 25.2% women took more than 1000 μg/d of FA supplements (3.5% consuming >5000 μg/d). In multivariate analysis, we observed that children whose mothers used FA supplement dosages higher than 5000 μg/d during pregnancy had a statistically significantly lower mean psychomotor scale score (difference, -4.35 points; 95% CI, -8.34 to -0.36) than children whose mothers used a recommended dosage of FA supplements (400-1000 μg/d). An increased risk of delayed psychomotor development (psychomotor scale score <85) was also evident among children whose mothers took FA supplement dosages higher than 5000 μg/d, although the association was not statistically significant (odds ratio = 1.59; 95% CI, 0.82-3.08). CONCLUSIONS AND RELEVANCE: To our knowledge, this is the first time a detrimental effect of high dosages of FA supplements during pregnancy on psychomotor development after the first year of life has been shown. Further research from longitudinal studies is warranted to confirm these results.

PMID: 25365251 [PubMed - indexed for MEDLINE]

2. The risk of abuse of vitamin supplements.

Ann Acad Med Stetin. 2014;60(1):60-4.

Marosz A, Chlubek D.

Abstract:
The article presents the results of studies on potential risks associated with the abuse of vitamin supplements which until recently had been considered not only highly effica- cious, but also completely safe. Particular consideration is given to vitamins A, E, D and C. The necessity to control the intake of vitamin supplements and even to strictly supervise the supply to high risk patients is highlighted.

PMID: 25518094 [PubMed - indexed for MEDLINE]

3. Liver injury from herbals and dietary supplements in the U.S. Drug-Induced Liver Injury Network.

Hepatology (2014) 60: 1399–1408. doi: 10.1002/hep.27317

Navarro, V. J., Barnhart, H., Bonkovsky, H. L., Davern, T., Fontana, R. J., Grant, L., Reddy, K. R., Seeff, L. B., Serrano, J., Sherker, A. H., Stolz, A., Talwalkar, J., Vega, M. and Vuppalanchi, R.

Abstract:
The Drug-Induced Liver Injury Network (DILIN) studies hepatotoxicity caused by conventional medications as well as herbals and dietary supplements (HDS). To characterize hepatotoxicity and its outcomes from HDS versus medications, patients with hepatotoxicity attributed to medications or HDS were enrolled prospectively between 2004 and 2013. The study took place among eight U.S. referral centers that are part of the DILIN. Consecutive patients with liver injury referred to a DILIN center were eligible. The final sample comprised 130 (15.5%) of all subjects enrolled (839) who were judged to have experienced liver injury caused by HDS. Hepatotoxicity caused by HDS was evaluated by expert opinion. Demographic and clinical characteristics and outcome assessments, including death and liver transplantation (LT), were ascertained. Cases were stratified and compared according to the type of agent implicated in liver injury; 45 had injury caused by bodybuilding HDS, 85 by nonbodybuilding HDS, and 709 by medications. Liver injury caused by HDS increased from 7% to 20% ($P < 0.001$) during the study period. Bodybuilding HDS caused prolonged jaundice (median, 91 days) in young men, but did not result in any fatalities or LT. The remaining HDS cases presented as hepatocellular injury, predominantly in middle-aged women, and, more frequently, led to death or transplantation, compared to injury from medications (13% vs. 3%; $P < 0.05$). *Conclusions*: The proportion of liver injury cases attributed to HDS in DILIN has increased significantly. Liver injury from nonbodybuilding HDS is more severe than from bodybuilding HDS or medications, as evidenced by differences in unfavorable outcomes (death and transplantation). (Hepatology 2014;60:1399–1408)

4. Hepatotoxicity of herbal and dietary supplements: an update.

Stickel F, Shouval D.

Arch Toxicol. 2015 Feb 14. [Epub ahead of print]

Abstract:
Herbal and dietary supplements (HDS) have been used for health-related purposes since more than 5000 years, and their application is firmly anchored in all societies worldwide. Over last decades, a remarkable renaissance in the use of HDS can be noticed in affluent societies for manifold reasons. HDS are forms of complementary and alternative medicines commonly used to prevent or treat diseases, or simply as a health tonic. Another growing indication for HDS is their alleged benefit for weight loss or to increase physical fitness. Access is easy via internet and mail-order pharmacies, and their turnover reaches billions of dollars in the USA and Europe alone. However, HDS are generally not categorized as drugs and thus less strictly regulated in most countries. As a result, scientific evidence proving their beneficial effects is mostly lacking, although some HDS may have purported benefits. However, the majority lacks such proof of value, and their use is predominantly based on belief and hope. In addition to missing scientific evidence supporting their use, HDS are typically prone to batch-to-batch variability in composition and concentration, contamination, and purposeful adulteration. Moreover, numerous examples of preparations emerged which have been linked to significant liver injury. These include single ingredients, such as kava, germander, and several Chinese herbals. Other HDS products associated with liver toxicity consist of multiple, often ill-defined ingredients, such as Hydroxycut and Herbalife. Affirmative diagnostic tests are not available, and the assessment of liver injury ascribed to HDS depends on a thorough and proactive medical history, careful exclusion of other causes, and a search for available reports on similar events linked to the intake of the suspected preparation or ingredients contained therein.

PMID: 25680499 [PubMed - as supplied by publisher]

5. Drug-induced liver injury: an overview over the most critical compounds.

Björnsson ES

Arch Toxicol. 2015 Mar;89(3):327-34. doi: 10.1007/s00204-015-1456-2. Epub 2015 Jan 25

Abstract:
There has been a substantial interest in drug-induced liver injury (DILI) recently. National Institutes of Health has sponsored a multicenter study in the USA for the last 10 years, which has collected valuable information in this context. Idiosyncratic DILI is like other adverse effects of drugs underestimated and underreported in most epidemiological studies. A recent prospective population-based study from Iceland found a crude incidence of approximately 19

cases per 100,000 and year. Antibiotic is the class of drugs most commonly implicated in patients with DILI. Amoxicillin-clavulanate continues to be the most commonly implicated agent occurring in approximately 1 out of 2,300 users. Drugs with the highest risk of DILI in the Icelandic study were azathioprine and infliximab. Although rare, statin-induced hepatotoxicity has been well documented. Liver injury associated with the use of herbal medicines and dietary supplements seems to be increasing. Information on the documented hepatotoxicity of drugs has recently been made easier by a website available in the public domain: LiverTox (http://livertox.nlm.nih.gov). Unfortunately, at the current time, pre-therapy risk assessment for DILI in the individual patient is difficult but previous well-documented hepatotoxicity is usually a contraindication for a subsequent treatment with the same drug.

PMID: 25618544 [PubMed - in process]

6. Drug-induced hepatotoxicity of select herbal therapies.

Korth C

J Pharm Pract. 2014 Dec;27(6):567-72. doi: 10.1177/0897190014546117.

Abstract:
The use of herbal botanicals and dietary supplements to treat and alleviate disease symptoms has increased over the past decades, and as a result, more research has been done to study the potential damaging effects of herbal products on the liver and other organs. Although reporting rates vary, cases have been published describing liver damage following herbal therapy. Studies have proposed multiple mechanisms of injury for these herbal preparations, and several potential risk factors have been identified including age, gender, polypharmacy, alcohol consumption, and genetic variability. Ingredients and other constituents often differ among products, and lack of standardization in manufacturing of these formulations makes it difficult to determine causality. The potential for drug-induced liver injury is often not known until the postmarketing period due to less rigorous safety testing and regulations.

PMID: 25546878 [PubMed - in process]

7. Data-driven identification of structural alerts for mitigating the risk of drug-induced human liver injuries.

Liu R, Yu X, Wallqvist A.

J Cheminform. 2015 Feb 11;7:4. doi: 10.1186/s13321-015-0053-y. eCollection 2015.

Abstract:
BACKGROUND: The use of structural alerts to de-prioritize compounds with undesirable features as drug candidates has been gaining in popularity. Hundreds of molecular structural moieties have been proposed as structural alerts. An emerging issue is that strict application of these alerts will result in a

significant reduction of the chemistry space for new drug discovery, as more than half of the oral drugs on the market match at least one of the alerts. To mitigate this issue, we propose to apply a rigorous statistical analysis to derive/validate structural alerts before use. METHOD: To derive human liver toxicity structural alerts, we retrieved all small-molecule entries from LiverTox, a U.S. National Institutes of Health online resource for information on human liver injuries induced by prescription and over-the-counter drugs and dietary supplements. We classified the compounds into hepatotoxic, nonhepatotoxic, and possible hepatotoxic classes, and performed detailed statistical analyses to identify molecular structural fragments highly enriched in the hepatotoxic class beyond random distribution as structural alerts for human liver injuries. RESULTS: We identified 12 molecular fragments present in multiple marketed drugs that one can consider as common "drug-like" fragments, yet they are strongly associated with drug-induced human liver injuries. Thus, these fragments may be considered as robust hepatotoxicity structural alerts suitable for use in drug discovery screening programs. CONCLUSIONS: The use of structural alerts has contributed to the identification of many compounds with potential toxicity issues in modern drug discovery. However, with a large number of structural alerts published to date without proper validation, application of these alerts may restrict the chemistry space and prevent discovery of valuable drugs. To mitigate this issue, we showed how to use statistical analyses to develop a small, robust, and broadly applicable set of structural alerts. Graphical abstractHepatotoxic-specific filters for flagging high risk compounds.

PMCID: PMC4339691

8. High-dose supplementation with vitamin C--induced pediatric urolithiasis: the first case report in a child and literature review.

Chen X, Shen L, Gu X, Dai X, Zhang L, Xu Y, Zhou P.

Urology. 2014 Oct;84(4):922-4. doi:10.1016/j.urology.2014.07.021. Review. PubMed PMID: 25260453.

Abstract:
High dose of vitamin C intake could increase urine oxalate excretion and hence the risk of calcium stone formation. We report a case of left ureteral stone in a 9-year-old boy with an extremely high urine oxalate excretion. Besides, he had a habit of taking high-dose supplementation of vitamin C since the age of 3 years. After vitamin C intake prohibited without other therapy and change of dietary intake, the urine oxalate excretion was decreased to normal level and no recurrence of urolithiasis was present during the 3-year follow-up. Thus, high-dose supplementation with vitamin C for years in a child could induce the urinary stones.

9. Garlic for the common cold.

Lissiman E, Bhasale AL, Cohen M.

Cochrane Database Syst Rev. 2014 Nov 11;11:CD006206. doi
10.1002/14651858.CD006206.pub4.

Update of Cochrane Database Syst Rev. 2012;3:CD006206.

Abstract:
Background Garlic is alleged to have antimicrobial and antiviral properties that relieve the common cold, among other beneficial effects. There is widespread usage of garlic supplements. The common cold is associated with significant morbidity and economic consequences. On average, children have six to eight colds per year and adults have two to four.Objectives To determine whether garlic (Allium sativum) is effective for the prevention or treatment of the common cold, when compared to placebo, no treatment or other treatments.Search methods We searched CENTRAL (2014, Issue 7),OLDMEDLINE (1950 to 1965),MEDLINE (January 1966 to July week 5, 2014), EMBASE(1974 to August 2014) and AMED (1985 to August 2014).Selection criteria Randomised controlled trials of common cold prevention and treatment comparing garlic with placebo, no treatment or standard treatment.Data collection and analysis Two review authors independently reviewed and selected trials from searches, assessed and rated study quality and extracted relevant data.Main results In this updated review, we identified eight trials as potentially relevant from our searches. Again, only one trial met the inclusion criteria.This trial randomly assigned 146 participants to either a garlic supplement (with 180 mg of allicin content) or a placebo (once daily)for 12 weeks. The trial reported 24 occurrences of the common cold in the garlic intervention group compared with 65 in the placebo group (P value < 0.001), resulting in fewer days of illness in the garlic group compared with the placebo
group (111 versus 366). The number of days to recovery from an occurrence of the common cold was similar in both groups (4.63 versus 5.63). Only one trial met the inclusion criteria, therefore limited conclusions can be drawn. The trial relied on self reported episodes of the common cold but was of reasonable quality in terms of randomisation and allocation concealment. Adverse effects included rash and odour. Authors' conclusions There is insufficient clinical trial evidence regarding the effects of garlic in preventing or treating the common cold. A single trial suggested that garlic may prevent occurrences of the common cold but more studies are needed to validate this finding. Claims of effectiveness appear to rely largely on poor-quality evidence.

PMID: 25386977 [PubMed - indexed for MEDLINE]

10. Astragalus (a traditional Chinese medicine) for treating chronic kidney disease.

Zhang HW, Lin ZX, Xu C, Leung C, Chan LS.

Cochrane Database Syst Rev. 2014 Oct 22;10:CD008369. doi:
10.1002/14651858.CD008369.pub2.

Abstract:
BACKGROUND: Astragalus (Radix Astragali, huang qi) is the dried root of Astragalus membranaceus (Fisch.) Bge. var. mongholicus (Bge.) Hsiao or Astragalus membranaceus (Fisch.) Bge. (Family Leguminosae). It is one of the most widely used herbs in traditional Chinese medicine for treating kidney diseases. Evidence

is needed to help clinicians and patients make judgments about its use for managing chronic kidney disease (CKD). OBJECTIVES: This review evaluated the benefits and potential harms of Astragalus for the treatment of people with CKD. SEARCH METHODS: We searched the Cochrane Renal Group's Specialised Register to 10
July 2014 through contact with the Trials' Search Co-ordinator using search terms relevant to this review. We also searched CINAHL, AMED, Current Controlled Trials, OpenSIGLE, and Chinese databases including CBM, CMCC, TCMLARS, Chinese Dissertation Database, CMAC and Index to Chinese Periodical Literature. SELECTION CRITERIA: Randomised controlled trials (RCTs) and quasi-RCTs comparing Astragalus, used alone as a crude herb or an extract, with placebo, no treatment, or conventional interventions were eligible for inclusion. DATA COLLECTION AND ANALYSIS: Two authors independently extracted data and assessed risk of bias in the included studies. Meta-analyses were performed using relative risk (RR) for dichotomous outcomes and mean differences (MD) for continuous outcomes, with 95% confidence intervals (CI).
MAIN RESULTS: We included 22 studies that involved 1323 participants, of whom 241 were receiving dialysis treatment. Risk of bias was assessed as high in six studies, and unclear in the remaining 16 studies. Study quality was low overall.Our nominated primary outcomes of time to requirement for renal replacement therapy (RRT) or initiation of dialysis and all-cause mortality were not reported in any of the included studies.Results concerning the effects of Astragalus on kidney function were inconsistent. Astragalus significantly increased CrCl at end of treatment (4 studies, 306 participants: MD 5.75 mL/min, 95% CI 3.16 to 8.34; I^2 = 0%), decreased SCr (13 studies, 775 participants: MD -21.39 μmol/L, 95% CI -34.78 to -8; I^2 = 70%) and especially in those whose baseline SCr was < 133 μmol/L in particular (3 studies, 187 participants: MD -2.52 μmol/l, 95% CI -8.47 to 3.42; I^2 = 0%). Astragalus significantly decreased 24 hour proteinuria at end of treatment (10 studies, 640 participants; MD -0.53 g/24 h, 95% CI -0.79 to -0.26; I^2 = 90%); significantly increased haemoglobin
levels overall (4 studies, 222 participants): MD 9.51 g/L, 95% CI 4.90 to 14.11; I^2 = 0%) and in haemodialysis patients in particular (3 studies, 142 participants: MD 11.20 g/L, 95% CI 5.81 to 16.59; I^2 = 0%). Astragalus significantly increased serum albumin (9 studies, 522 participants: MD 3.55 g/L, 95% CI 2.33 to 4.78; I^2 = 65%). This significant increase was seen in both dialysis (3 studies, 152 participants): MD 4.04 g/L, 95% CI 1.91 to 6.16; I^2 = 72%) and non-dialysis patients (6 studies, 370 participants: MD 3.24 g/L, 95% CI 1.70 to 4.77; I^2 = 61%). Astragalus significantly decreased systolic blood
pressure (2 studies, 77 participants: MD -16.65 mm Hg, 95% CI -28.83 to -4.47; I^2 = 50%), and diastolic blood pressure (2 studies, 77 participants: MD -6.02 mm Hg, 95% CI -10.59 to -1.46; I^2 = 0%).Six of 22 included studies reported no adverse effects were observed; while the remaining 16 studies did not report adverse effects. AUTHORS' CONCLUSIONS: Although Astragalus as an adjunctive treatment to conventional therapies was found to offer some promising effects in reducing proteinuria and increasing haemoglobin and serum albumin, suboptimal methodological quality and poor reporting meant that definitive conclusions could not be made based on available evidence.

PMID: 25335553 [PubMed - indexed for MEDLINE]