Probiotics for non-alcoholic fatty liver disease and/or steatohepatitis (Review)

Lirussi F, Mastropasqua E, Orando S, Orlando R

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TABLE OF CONTENTS

[Intervention Review]

Probiotics for non-alcoholic fatty liver disease and/or steatohepatitis

Flavio Lirussi[1], Ezio Mastropasqua[2], Serena Orando[3], Rocco Orlando[4]

[1]Scientist, Socioeconomic Determinants of NCDs, WHO Regional Office for Europe, European Office for Investment for Health and Development, Venice, Italy. [2]Ospedale di Este, Padova, Italy. [3]Instituto di Anestesia e Rianimazione, Universitá Degli Studi di Firenze, Firenze, Italy. [4]Department of Medical and Surgical Sciences, University of Padua Medical School, Padova, Italy

Contact address: Flavio Lirussi, Scientist, Socioeconomic Determinants of NCDs, WHO Regional Office for Europe, European Office for Investment for Health and Development, Campo Santo Stefano, San Marco 2847, Venice, I-30124, Italy. fli@ihd.euro.who.int.

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ABSTRACT

Background

Non-alcoholic fatty liver disease comprises a spectrum of diseases ranging from simple steatosis to non-alcoholic steatohepatitis, fibrosis, and cirrhosis. Probiotics have been proposed as a treatment option because of their modulating effect on the gut flora that could influence the gut-liver axis.

Objectives

To evaluate the beneficial and harmful effects of probiotics for non-alcoholic fatty liver disease and/or steatohepatitis.

Search methods

We searched *The Cochrane Hepato-Biliary Group Controlled Trials Register* (July 2006), the *Cochrane Central Register of Controlled Trials* (*CENTRAL*) in *The Cochrane Library* (Issue 2, 2006), *MEDLINE* (1966 to May 2006), and *EMBASE* (1980 to May 2006). No language restrictions were applied.

Selection criteria

Randomised clinical trials evaluating probiotic treatment in any dose, duration, and route of administration versus no intervention, placebo, or other interventions in patients with non-alcoholic fatty liver disease. The diagnosis was made by history of minimal or no alcohol intake, imaging techniques showing hepatic steatosis and/or histological evidence of hepatic damage, and by exclusion of other causes of hepatic steatosis.

Data collection and analysis

We had planned to extract data in duplicate and analyse results by intention-to-treat.

Main results

No randomised clinical trials were identified. Preliminary data from two pilot non-randomised studies suggest that probiotics may be well tolerated, may improve conventional liver function tests, and may decrease markers of lipid peroxidation.

Authors' conclusions

The lack of randomised clinical trials makes it impossible to support or refute probiotics for patients with non-alcoholic fatty liver disease and non-alcoholic steatohepatitis.

PLAIN LANGUAGE SUMMARY

No evidence to support or refute probiotics for patients with non-alcoholic fatty liver disease and/or steatohepatitis

Probiotics have been proposed as a treatment option for patients with non-alcoholic fatty liver disease and non-alcoholic steatohepatitis because of their balancing role on the flora of the gut that may act as a potential source of hepatotoxic oxidative injury. This review did not identify any randomised clinical trials with probiotics in non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. Even if the results from pilot studies seem promising, randomised clinical trials are necessary to asses the clinical implication of probiotics therapy in non-alcoholic fatty liver disease and non-alcoholic steatohepatitis.

BACKGROUND

Non-alcoholic fatty liver disease (NAFLD) is a disorder with histologic features of alcohol-induced fatty liver disease in individuals who consume little or no alcohol. It affects 3% to 25% of the general population (Lonardo 1999; Angulo 2002; Clark 2006). Histologically NAFLD ranges from simple steatosis to non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and hepatocellular carcinoma (Angulo 2002; Neuschwander-T 2003; Liou 2006). NAFLD is usually associated with a number of diseases such as obesity, type 2 diabetes mellitus, hyperlipidaemia, coeliac disease, exposure to various drugs and toxins, and surgical procedures (jejuno-ileal bypass and other operations on the gastrointestinal tract) (Burt 1998; Angulo 2002; Chitturi 2002; Younossi 2002). The prevalence of coeliac disease, which may increase intestinal permeability, is about 3% in patients with NAFLD (Grieco 2001; Bardella 2004). It is still unknown whether *Helicobacter pylori* infection, which can also be associated with increased mucosal permeability of the gut (Fukuda 2001), may promote the development of NAFLD.

The natural history of NAFLD is uncertain. Patients with fatty liver alone have a benign long-term prognosis (Day 2006), whereas non-alcoholic steatohepatitis (NASH) patients show a much more aggressive course, with development of cirrhosis in up to 26% of patients (Angulo 1999; Ratziu 2000; Dixon 2001; Day 2006). Indeed, a number of studies suggest that NAFLD may be responsible for cryptogenic cirrhosis (Brolin 1998; Calwell 1999; Poonawala 2000; Liou 2006).

The pathophysiology of NAFLD is believed to entail two steps. The first step involves insulin resistance, which induces the development of steatosis. The second step is oxidative stress that activates an inflammatory response and causes NASH (Chitturi 2001; McCullough 2002; McCullogh 2006). Additional insults, such as exposure to lipopolysaccharide, certain hepatotoxins, or infectious agents, may also lead to the development of cirrhosis (Diehl 2000; Medina 2004).

An interesting animal model for the study of the disease is represented by leptin-deficient, insulin-resistant *ob/ob* mice that develop NAFLD spontaneously (Koteish 2001). These animals have an increased endogenous production of ethanol due to intestinal bacterial overgrowth (Cope 2000). Ethanol not only is hepatotoxic, but also increases intestinal permeability, thus enhancing hepatic exposure to other gut bacterial products, such as lipopolysaccharide. Both ethanol- and lipopolysaccharide-related liver damage require the induction of tumour necrosis factor-alfa (TNF-alfa), a proinflammatory cytokine that also produces apoptosis. Indeed, elevated levels of TNF-alfa and a higher prevalence of intestinal bacterial overgrowth have been reported in NASH patients compared to controls (Wigg 2001; Riordan 2002). Intestinal bacterial overgrowth has also been reported in patients with jejuno-ileal bypass, with small bowel diverticulosis, on long-term total parenteral nutrition, and in those with diabetes mellitus (Nazim 1989; Wigg 2001), all of whom may develop hepatic steatosis or NASH. Possible factors involved are: lessening of intestinal motility (Crowell 1994); excessive consumption of dietary carbohydrate (Hunnisett 1990); abnormalities in the development of gut-associated lymphoid tissue at an early age (Hooper 2001); and TNF-alfa gene polymorphism (Valenti 2002). Further evidence of the link between intestinal bacterial overgrowth and hepatic damage is based on the following observations:

(1) Oral administration of neomycin in ob/ob mice significantly reduces breath ethanol levels (Cope 2000);

(2) Antibiotics (metronidazole and tetracycline) reduce hepatic injury in rats with surgically induced intestinal bacterial overgrowth (Lichtman 1991);

(3) Metronidazole prevents and reverses hepatic steatosis after intestinal bypass for morbid obesity in man (Drenick 1982).

These findings imply a critical role for small bowel flora, suggesting that intestinal bacterial overgrowth treatment might reduce ethanol and lipopolysaccharide levels. Probiotics, which are live microbial food supplements or components of bacteria (Salminen 1998), may have beneficial effects on human health and have no known negative long-term effects. Moreover, they cause anti-inflammatory responses and protect gut epithelial cells from invasion and adhesion of different pathogens (Solga 2003; Ghosh 2004), including *Helicobacter pylori* (Hamilton-Miller 2003). Their effect on gut permeability remains controversial (Kennedy 2000; Gotteland 2001; Mangell 2002; Resta-Lenert 2003). Probiotics are widely used to treat infectious diarrhoea (Guandalini 2000; Gionchetti 2002) and have been reported to be effective in preventing relapse in ulcerative colitis (Venturi 1999). Moreover, several studies demonstrate that probiotics reduce the risk of pouchitis (Gionchetti 2000). Probiotics might decrease inflammation and therefore improve NAFLD by the following mechanisms (Solga 2003):

(1) Competitive inhibition and possible exclusion of pathogenic strains of intestinal bacterial overgrowth, especially strains that have lower total in vitro binding capacity (Lee 2000).

(2) Alteration of the inflammatory effects of pathogenic intestinal bacterial overgrowth through changes in cytokines signalling (Madsen 2001).

(3) Improved epithelial barrier function by modulating cytoskeletal and tight junctional protein phosphorylation (Resta-Lenert 2003; Ghosh 2004).

(4) Direct decrease in proinflammatory cytokines, eg, TNF-alfa (Li 2003).

(5) Stimulation of IgA production (Gronlund 2000).

We have been unable to identify any meta-analysis or systematic reviews on probiotics for patients with patients with NAFLD and/or NASH.

OBJECTIVES

To assess the beneficial and harmful effects of probiotics for NAFLD and/or NASH.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised clinical trials, regardless of publication status, number of patients randomised, language, or blinding.

Types of participants

Participants of any age, sex, or ethnic origin with NAFLD, including NASH and cryptogenic cirrhosis, diagnosed on the basis of the following criteria:
(1) Imaging techniques showing evidence of hepatic steatosis or steatofibrosis and/or liver biopsy showing histological alterations including simple steatosis, fatty infiltration plus nonspecific inflammation, steatohepatitis, fibrosis, and cirrhosis.
(2) Daily alcohol intake less than 20 g in women and 40 g in men (Becker 1996; Neuschwander-T 2003).
(3) Exclusion of other causes of hepatic steatosis or steatofibrosis including hepatitis B, hepatitis C, autoimmune hepatitis, and genetic liver disease such as Wilson's disease and haemochromatosis. Participants presenting one or more causes commonly associated with secondary NAFLD (drugs and miscellaneous disorders such as a- or hypo-beta lipoproteinemia, partial lipodystrophy, environmental toxins, or total parenteral nutrition) were also to be excluded.

Types of interventions

Probiotics (*Lactobacillus*, *Bifidobacterium*, and other live microbial food supplements or components) at any dose, duration, and route of administration, given separately or in combination versus no intervention, placebo, or other interventions. Co-interventions were also to be considered when used equally in both intervention arms.

Types of outcome measures

Primary outcome measures
(1) All-cause mortality: number of deaths irrespective of cause.
(2) Hepatic-related mortality.
(3) Radiological response (degree of fatty liver infiltration assessed by ultrasound, computer tomography scanning, nuclear magnetic resonance, or other imaging techniques) and/or histological response (number of patients with histological improvement/deterioration and changes in the degree of fatty liver infiltration, inflammation, and fibrosis) based on Brunt system or its modifications (Brunt 2001; Harrison 2003).
Secondary outcome measures
(4) Biochemical response (serum activities of aspartate aminotransferase, alanine aminotransferases, alkaline phosphatases, gamma-

glutamyl-transpeptidase, serum total bilirubin, ferritin, and fasting lipid profiles).
(5) Breath tests (breath ethanol, carbon dioxide levels, D-xylose-lactulose, or other markers of intestinal bacterial overgrowth) (Nazim 1989; Wigg 2001).
(6) Adverse events (any adverse events as reported in trials). Depending on availability of data, we planned to classify adverse events as serious or non-serious. Serious adverse events were to be defined as any untoward medical occurrence that was life threatening, resulted in death or persistent or significant disability, or any medical event which might have jeopardised the patient or required intervention to prevent it. All other adverse events were to be considered non-serious.
(7) Quality-of-life measures.
(8) Cost-effectiveness.

Search methods for identification of studies

We searched *The Cochrane Hepato-Biliary Group Controlled Trials Register* (July 2006), the *Cochrane Central Register of Controlled Trials* (*CENTRAL*) in *The Cochrane Library* (Issue 2, 2006), *MEDLINE* (1966 to May 2006), *EMBASE* (1966 to May 2006). See Appendix 1 for the search strategies that we applied to the individual databases.

Data collection and analysis

We planned to follow the instructions given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2006) and the *Cochrane Hepato-Biliary Group Module* (Gluud 2006).

Trial selection

Two authors (SO and EM) independently assessed whether the identified studies fulfilled the inclusion criteria. Excluded trials were listed in 'Characteristics of excluded studies', with reasons for exclusion being reported accordingly. Since no randomised clinical trials were identified, data extraction, evaluation of methodological quality, and statistical analyses could not be performed.
The following part of the protocol could not be followed because randomised clinical trials that would fulfil the inclusion criteria described in the present protocol could not be found. This is the reason why we have kept the text in future tense and we will change the tense accordingly when trials fulfilling the inclusion criteria are identified in the future.

Methodological quality of included studies

We will define the methodological quality as the confidence that the design and report will restrict bias in the intervention comparison (Moher 1998; Kjaergard 2001). Due to the risk of overestimation of intervention effects in randomised trials with inadequate methodological quality (Schulz 1995; Moher 1998; Kjaergard 2001), we will assess the influence of methodological quality on the treatment effects of probiotics.

Generation of the allocation sequence

- Adequate, if the allocation sequence was generated by a computer or random number table. Drawing of lots, tossing of a coin, shuffling of cards, or throwing dice will be considered as adequate if a person who was not otherwise involved in the recruitment of participants performed the procedure.
- Unclear, if the trial was described as randomised, but the method used for the allocation sequence generation was not described.
- Inadequate, if a system involving dates, names, or admittance numbers were used for the allocation of patients. These studies are known as quasi-randomised and will be excluded from the present review when assessing beneficial effects.

Allocation concealment

- Adequate, if the allocation of patients involved a central independent unit, on-site locked computer, identically appearing numbered drug bottles or containers prepared by an independent pharmacist or investigator, or sealed envelopes.
- Unclear, if the trial was described as randomised, but the method used to conceal the allocation was not described.
- Inadequate, if the allocation sequence was known to the investigators who assigned participants or if the study was quasi-randomised.

Blinding (or masking)

- Adequate, if the trial was described as double blind and the method of blinding involved identical placebo or active drugs.
- Unclear, if the trial was described as double blind, but the method of blinding was not described.
- Not performed, if the trial was not double blind.

Follow-up

- Adequate, if the numbers and reasons for dropouts and withdrawals in all intervention groups were described or if it was specified that there were no dropouts or withdrawals.
- Unclear, if the report gave the impression that there had been no dropouts or withdrawals, but this was not specifically stated.
- Inadequate, if the number or reasons for dropouts and withdrawals were not described.

Furthermore, we will register whether or not the randomised clinical trials have used an intention-to-treat analysis (Gluud 2001) and sample-size calculation.
In case data have not been reported sufficiently or are not published at all, we will seek further information by correspondence with the authors.

Analyses and presentation

We will perform the meta-analyses according to the recommendations of The Cochrane Collaboration (Higgins 2006).
We will use the software package RevMan 4.2 provided by The Cochrane Collaboration (RevMan 2003). For dichotomous vari-

ables, we will calculate the relative risks with 95% confidence interval. We will use a random-effects model (DerSimonian 1986) and a fixed-effect model (DeMets 1987). In case of discrepancy between the two models we will report both results, otherwise we will report only the results from the fixed-effect model.

We will perform subgroup analyses depending on the methodological quality of the trials in order to compare the intervention effect in trials with adequate methodological quality to that of trials with unclear or inadequate methodological quality. Heterogeneity will be explored by chi-squared test with significance set at P value 0.10 and the quantity of heterogeneity will be measured by I^2 (Higgins 2002).

Regarding the primary outcome measure, we will include patients with incomplete or missing data in the sensitivity analyses by imputing them (Hollis 1999). This kind of approach, as part of sensitivity analyses, will allow to evaluate the robustness of the findings of a meta-analysis as follows:

- Available case analysis: data on only those whose results are known, using as denominator the total number of patients who completed the trial;
- Assuming poor outcome: dropouts from both the probiotics group and control group had the primary outcomes;
- Assuming good outcome: none of the dropouts from the probiotics group and control group had the primary outcomes;
- Extreme case favouring probiotics: none of the dropouts from the probiotics group but all of the dropouts from the control group had the first two primary outcomes, and all of the probiotic patients but none of the controls responded.
- Extreme case favouring control: all dropouts from the probiotics group but none from the control group had the first two primary outcomes, and all of the controls but none of the probiotic patients responded.

For the secondary outcomes, we will adopt 'available case analysis'.

Bias exploration

Funnel plot will be used to provide a visual assessment of whether treatment estimates are associated with study size. The performance of the available methods of detecting biases (Begg 1994; Egger 1997; Macaskill 2001) vary with the magnitude of the treatment effect, the distribution of study size, and whether a one- or two-tailed test is used (Macaskill 2001). Therefore, we will use the most appropriate method, which has good trade-off in the sensitivity and specificity based on characteristics of the trials to be included in our review.

RESULTS

Description of studies

See: Characteristics of excluded studies.

The electronic searches of *The Cochrane Hepato-Biliary Group Controlled Trials Register* and the *Cochrane Central Register of Controlled Trials* (*CENTRAL*) in *The Cochrane Library* did not produce any references. By searching *MEDLINE* and *EMBASE* we retrieved 91 and 297 references, respectively. Of these, we excluded 386 duplicated or clearly irrelevant references (NASH is also a surname, a reagent, and a general hospital). Thus only two references of possible interest were identified and retrieved for evaluation. Both of these studies (Loguercio 2002; Loguercio 2005), however, were excluded because they did not fulfil our inclusion criteria.

In addition, we wrote to lead authors working on probiotics in experimental animals, asking them whether they were carrying out studies on the present topic in humans. They replied that no studies of this kind were in progress.

Risk of bias in included studies

No randomised clinical trials were found.

Effects of interventions

We could not find any randomised clinical trials that fulfilled the inclusion criteria of our protocol (Lirussi 2005).

We identified two non-randomised clinical studies on probiotics in chronic liver diseases of different aetiology, including NAFLD (see description under Excluded studies).

DISCUSSION

In our search we did not find any randomised clinical trials evaluating probiotics as a therapy for NAFLD or NASH. We only identified small non-randomised studies suggesting that probiotics were not associated with frequent severe adverse effects. Due to the design of these studies we have no knowledge on any potential beneficial or harmful effects.

Animal studies support a pathogenetic role of intestinal bacterial overgrowth for hepatic steatosis, and some beneficial effects of probiotics on liver function tests in this pathological condition (Lichtman 1991; Pappo 1991; Li 2003). These studies suggest the presence of an interaction between the intestinal lumen and the liver. In fact, the intestinal flora can increase the release of pro-inflammatory and pro-fibrotic cytokines, thus contributing to the development of liver damage. Probiotics could, therefore, act by inhibiting the growth of pathological strains, improving epithelial barrier function and changing cytokine signalling (Solga 2003). Intestinal microflora can also influence liver function via endotoxins production (ethanol, ammonium and acetaldehyde). Release of endotoxins modulate Kupffer cells activity and hepatic cytokine

production. Thus, probiotics could be considered a potential tool for the prevention and treatment of NASH.

NASH is frequently seen in patients with jejuno-ileal bypass performed for severe obesity and patients in jejunal diverticulosis. Both conditions favour bacterial bacterial overgrowth of the small intestine. Intestinal bacterial overgrowth is more frequent in NASH patients than in controls (Wigg 2001). Moreover, there is evidence that oro-cecal transit time is increased in patients with NAFLD, thus supporting the link between endotoxin-induced liver damage and intestinal bacterial overgrowth (Soza 2005). Antibiotics active on the intestinal microflora are claimed to improve hepatic steatosis in humans receiving total parenteral nutrition (Pappo 1992). However, in a recent study, norfloxacin administration had no effect on alanine aminotransferase levels, lactulose breath test, and anti-endotoxin core antibodies titers in nondiabetic patients with NAFLD (Soza 2005).

The results obtained in the two pilot studies of this review seem promising. They suggest a possible therapeutic role of probiotics in the treatment of a number of chronic liver diseases, including NAFLD. However, despite the rationale for the use of probiotics based on studies in both animals and man, no controlled trials have been performed so far in patients with NAFLD/NASH. We, therefore, need randomised clinical trials of adequate size and methodology assessing the potential beneficial and harmful effect of probiotics. Other points that need to be clarified before probiotics can be considered for clinical practice relate to the type of preparation to be administered (single or multiple strains), the concentration of bacteria, the duration of therapy, and the maintenance of the favourable effect, if any. Some more technical aspects, such as viability of microorganisms during preparation and storage, should also be clarified.

AUTHORS' CONCLUSIONS

Implications for practice

The lack of randomised clinical trials makes it impossible to asses the effect of probiotics administration in patients with NAFLD/NASH. There are no data to support or refute the use of probiotics in clinical practice. We, therefore, suggest that probiotics should not be used for this condition outside randomised clinical trials.

Implications for research

Randomised clinical trials on probiotics are needed to examine their role as therapy in NAFLD/NASH. The trials need to be of adequate size and adequate methodology and have to be registered in a public register associated with the World Health Organization's platform for registration of clinical trials before inclusion of the first participant, and reported according to the CONSORT guidelines (http://www.consort-statement.org).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Loguercio 2002	Pilot study; not a randomised trial. Loguercio 2002 et al tested a mixture of different bacteria strains called LAB (Lactobacillus acidophilus, Bifidus, Rhamnosus, Plantarum, Salivarius, Bulgaricus, Lactis, Casei, Breve) associated to fructo-oligo-saccharides as prebiotic, vitamins (B6, B2, B12, D3, C, folic acid), as well as trace elements. Three groups of patients were enrolled in the study: 12 patients with biopsy-proven chronic hepatitis C, 10 patients with alcoholic cirrhosis all of whom continued drinking alcohol in excess, and 10 patients with biopsy-proven NASH. The NASH patients (all men) were treated with LAB for two months. After treatment, lipid peroxidation indices - malondialdehyde and 4-hydroxinonenal - decreased by 62% and 45%, respectively. TNF-a levels decreased by 18 %
Loguercio 2005	Pilot study; not a randomised trial. Loguercio 2005 et al evaluated probiotic therapy in patients with various hepatic diseases. A total of 78 patients were enrolled in the study. Forty-two had a biopsy-proven diagnosis of NAFLD (22) or HCV-related chronic hepatitis (20), whereas the remaining 36 had either a clinical diagnosis of alcoholic liver cirrhosis (20) or HCV-related cirrhosis (16). NAFLD group was younger than the other groups: 37 years versus 50, 52, 59 in alcoholic cirrhosis, HCV-related chronic hepatitis and cirrhosis, respectively. All patients were treated for three months with the probiotic VSL3#, a mixture containing 450 billions of bacteria different strains. Biochemical tests were performed at baseline, at 90 days, and 120 days after starting probiotics. These included routine liver function tests, cytokines (TNF-alfa, interleukin-6, interleukin-10), markers of lipid peroxidation (malonildialdehyde, 4-hydroxinonenal), and S-nitrosothiols, a marker of nitric oxide metabolism. The mixture was well tolerated in all groups with only 4 dropouts because of drug intolerance (meteorism and diarrhoea). Aminotransferase plasma levels significantly decreased in all groups after VSL3# treatment, the effect being maintained after one month of washout in HCV-related chronic hepatitis, NAFLD, and alcoholic cirrhosis groups. Patients with alcoholic cirrhosis exhibited also a significant and persistent decrease of gammaglutamyltranspeptidase. Plasma levels of TNF-alfa, IL-6, and IL-10 did not change significantly in NAFLD patients compared to baseline. Malonildialdehyde and 4-hydroxinonenal were significantly decreased in NAFLD and in alcoholic cirrhosis both at 90 days and 120 days during treatment. S-nitrosothiols plasma levels, elevated in all groups of patients at baseline, showed a significant decrease during treatment, persisting also during the washout period in all groups

NASH = non-alcoholic steatohepatitis
NAFLD = non-alcoholic fatty liver disease

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. Search strategies

Database	Date of search	Search strategy
The Cochrane Hepato-Biliary Group Specialised Register	July 2006.	probiotic* AND steatohepatitis AND nonalcoholic fatty liver disease
The Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library	Issue 2, 2006.	probiotic* AND steatohepatitis AND nonalcoholic fatty liver disease
MEDLINE	1966 to May 2006.	(probiotic* OR "natural supplements" OR Lactobacill* OR "Lactococcus lactis" OR "lactic acid bacteria" OR Bifidobacteri* OR VSL#* OR LAB OR Bacterioides OR Clostridium OR Fusobacterium OR Eubacterium OR Peptococcus OR Peptostreptococcus OR Escherichia OR E.Coli OR Veillonella OR Streptococc* OR Saccharomyces OR "Enterococcus faecium" OR "aerobic bacteria*" OR "anaerobic bacteria*" OR microrganism* OR bacteria OR microflora OR "gut microecology" OR "intestinal bacteria*" OR "intestinal flora" OR "commensal bacteria" OR "small bowel bacterial overgrowth" OR "intestinal bacterial overgrowth" OR SIBO OR SBBO OR IBO OR endotoxaemia OR endotoxin* OR "enteric bacterial product*" OR "ethanol test") AND ("non*alcoholic fatty liver" OR "non alcoholic fatty liver" OR "nonalcoholic fatty liver" OR NAFL* OR NASH OR steatohepatitis) NOT "NASH A" NOT "NASH AA" NOT "NASH AD" NOT "NASH AS" NOT "NASH B" NOT "NASH BR" NOT "NASH BW" NOT "NASH C" NOT "NASH CB" NOT "NASH CH" NOT "NASH CL" NOT "NASH CR" NOT "NASH CW" NOT "NASH D" NOT "NASH DC" NOT "NASH DF" NOT "NASH DL" NOT "NASH DR" NOT "NASH DT" NOT "NASH E" NOT "NASH EC" NOT "NASH EJ" NOT "NASH ES" NOT "NASH FD" NOT "NASH FW" NOT "NASH G" NOT "NASH GB" NOT "NASH General Hospital" NOT "NASH GL" NOT "NASH GS" NOT "NASH GV" NOT "NASH H" NOT "NASH HA" NOT "NASH Hall" NOT "NASH HD" NOT "NASH HM" NOT "NASH HW" NOT "NASH J" NOT "NASH JB" NOT "NASH JE" NOT "NASH JF" NOT "NASH JH" NOT

(*Continued*)

		"NASH JJ" NOT "NASH JM" NOT "NASH JQ" NOT "NASH JR" NOT "NASH JW" NOT "NASH K" NOT "NASH KA" NOT "NASH KL" NOT "NASH L" NOT "NASH LD" NOT "NASH LJ" NOT "NASH M" NOT "NASH MA" NOT "NASH MC" NOT "NASH ML" NOT "NASH MM" NOT "NASH MW" NOT "NASH N" NOT "NASH P" NOT "NASH PB" NOT "NASH PJ" NOT "NASH PP" NOT "NASH R" NOT "NASH RA" NOT "NASH reaction" NOT "NASH reagent" NOT "NASH RJ" NOT "NASH RS" NOT "NASH RW" NOT "NASH S" NOT "NASH SA" NOT "NASH SM" NOT "NASH solution" NOT "NASH SV" NOT "NASH T" NOT "NASH TA" NOT "NASH TC" NOT "NASH TD" NOT "NASH TE" NOT "NASH TG" NOT "NASH TL" NOT "NASH TW" NOT "NASH University" NOT "NASH W" NOT "NASH WA" NOT "NASH WG"
EMBASE	1980 to May 2006.	1 probiotic* 2 "natural" 3 "supplements" 4 Lactobacill* 5 "Lactococcus" 6 "lactis" 7 "lactic" 8 "acid" 9 "bacteria" 10 Bifidobacteri* 11 VSL* 12 LAB 13 Bacterioides 14 Clostridium 15 Fusobacterium 16 Eubacterium 17 Peptococcus 18 Peptostreptococcus 19 probiotic* or "natural supplements" or Lactobacill* or "Lactococcus lactis" or "lactic acid bacteria" or Bifidobacteri* or VSL* or LAB or Bacterioides or Clostridium or Fusobacterium or Eubacterium or Peptococcus or Peptostreptococcus 20 Escherichia 21 E.Coli 22 Veillonella 23 Streptococc* 24 Saccharomyces 25 "Enterococcus" 26 "faecium" 27 "aerobic" 28 "bacteria*" 29 "anaerobic"

(*Continued*)

		30 “bacteria*” 31 microrganism* 32 bacteria 33 Escherichia or E.Coli or Veillonella or Streptococc* or Saccharomyces or “Enterococcus faecium” or “aerobic bacteria*” or “anaerobic bacteria*” or microrganism* or bacteria 34 microflora 35 “gut” 36 “microecology” 37 “intestinal” 38 “bacteria*” 39 “intestinal” 40 “flora” 41 “commensal” 42 “bacteria” 43 “small” 44 “bowel” 45 “bacterial” 46 “overgrowth” 47 “intestinal” 48 “bacterial” 49 “overgrowth” 50 microflora or “gut microecology” or “intestinal bacteria*” or “intestinal flora” or “commensal bacteria” or “small bowel bacterial overgrowth” or “intestinal bacterial overgrowth” 51 SIBO 52 SBBO 53 IBO 54 endotoxaemia 55 endotoxin* 56 “enteric” 57 “bacterial” 58 “product*” 59 “ethanol” 60 “test” 61 #50 or SIBO or SBBO or IBO or endotoxaemia or endotoxin* or “enteric bacterial product*” or “ethanol test” 62 “non*alcoholic” 63 “fatty” 64 “liver” 65 “non” 66 “alcoholic” 67 “fatty” 68 “liver” 69 “nonalcoholic” 70 “fatty” 71 “liver” 72 NAFL*

(*Continued*)

		73 NASH 74 steatohepatitis 75 "non*alcoholic fatty liver" or "non alcoholic fatty liver" or "nonalcoholic fatty liver" or NAFL* or NASH or steatohepatitis 76 #19 or #33 or #50 or #61 77 #75 and #76

WHAT'S NEW

Last assessed as up-to-date: 12 November 2006.

Date	Event	Description
9 November 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 2005

Review first published: Issue 1, 2007

CONTRIBUTIONS OF AUTHORS

F Lirussi and S Orando formulated the idea for the review, and revised the protocol and the review. E Mastropasqua and S Orando developed and tested the search strategies for the review, selected trials for the review, and retrieved the data. All authors contributed to the writing of the review.

DECLARATIONS OF INTEREST

None known.

INDEX TERMS

Medical Subject Headings (MeSH)

Fatty Liver [*therapy]; Probiotics [*therapeutic use]

MeSH check words

Humans