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**Efficacy of fermented milk and whey proteins in *helicobacter pylori* eradication, a review**

Sachdeva A *et al*. Fermented milk in *H.* *pylori* eradication

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**Abstract**

*Helicobacter pylori* (*H. pylori*) eradication is considered a necessary step in the management of peptic ulcer disease, chronic gastritis, gastric adenocarcinoma and mucosa associated lymphoid tissue lymphoma. Standard triple therapy eradication regimens are inconvenient and achieve unpredictable and often poor results. Further, the rates are decreasing over time with increase in antibiotic resistance. Fermented milk and several of its component whey proteins have emerged as candidates for complementary therapy. In this context the current review seeks to summarize the current evidence available on their role in *H. pylori* eradication. Pertinent narrative/systematic reviews, clinical trials and laboratory studies on individual components including fermented milk, yogurt, whey proteins, lactoferrin, α-lactalbumin, glycomacropeptide and immunoglobulin were comprehensively searched and retrieved from Medline, Embase, Scopus, Cochrane Controlled Trials Register and abstracts/ proceedings of conferences up to May 2013. A preponderance of the evidence available on fermented milk based probiotic preparations and bovine lactoferrin suggests a beneficial effect in helicobacter eradication. Evidence for alpha-lactalbumin and immunoglobulins is promising while that for glycomacropeptide is preliminary and requires substantiation. The magnitude of the potential benefit documented so far is small and the precise clinical settings are ill defined. This restricts the potential use of this group as a complementary therapy in a nutraceutical setting hinging on better patient acceptability/compliance. Further work is necessary to identify the optimal substrate, fermentation process, dose of administration and the ideal clinical setting (prevention/treatment, first line therapy/recurrence, symptomatic/asymptomatic, gastritis/ulcer diseases *etc.*). The potential of this group in a high antibiotic resistance or treatment failure settings presents interesting possibilities and deserves further exploration.

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**Key words:** *Helicobacter pylori*; fermented milk; whey proteins; bovine lactoferrin; α-Lactalbumin; glycomacropeptide; immunoglobulin

**Core tip:** Treatment regimens for *Helicobacter* are cumbersome, prone to side effects and often have low success rates. Fermented milk and related proteins have often been explored as potential candidates for complementary therapy. The current review sought to summarize the current evidence available on their role in *Helicobacter pylori* eradication and found substantial evidence to support the use of fermented milk based probiotic preparation and bovine lactoferrin. Evidence for other whey proteins is preliminary and requires substantiation. Further work is necessary to identify the optimal substrate, fermentation process, dose and the ideal clinical setting. The potential of this group in antibiotic resistance or treatment failure settings also presents interesting possibilities.

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**INTRODUCTION**

*Helicobacter pylori* (*H. pylori)* is a gram negative, spiral shaped bacterium found in the gastric mucous layer. It has an ammonia-producing surface urease which allows adherence to and colonization of the gastric epithelium, by neutralizing the acidic gastric environment[1]. *H. pylori* is now implicated in peptic ulcer disease, chronic gastritis, gastric adenocarcinoma and mucosa associated lymphoid tissue lymphoma and duodenal ulcer disease[2-4]. Eradication of *H. pylori* is considered a necessary step in the management of these diseases. Standard triple therapy eradication regimens (proton pump inhibitor plus clarithromycin and amoxicillin or nitroimidazole) are inconvenient and achieve unpredictable and often poor results[5]. Further, eradication rates are reported to be decreasing over time with increase in antibiotic resistance[6]. The second line quadruple regimens are further limited by poorer patient compliance and increased side effects[6]. In this context, several alternative and complimentary therapies have been tried in an attempt to achieve better eradication without affecting compliance. In this search, fermented milk and several of its component whey proteins have emerged as potential candidates for complementary therapy. They have the inherent advantage of better patient acceptability.

Several randomized controlled trials and a recent metanalysis document that fermented milk based probiotic preparations improve *H. pylori* eradication rates by 10%. Their efficacy has been argued to be better than capsule-based bacteria-only preparations and considered partly or completely contributed by the anti-bacterial and immunogenic properties of component whey proteins formed as a result of fermentation *etc*. Potential efficacy of individual whey proteins in *H. pylori* eradication has also been a subject of interest in recent research. However the role of fermented milk or whey proteins in clinical practice is not yet universally accepted, precisely defined or widely discussed[7]. In this context the current review sought to summarize the current evidence available on the role of fermented milk and its component whey proteins in *H. pylori* eradication.

For the purpose of the current review pertinent narrative/systematic reviews, clinical trials and laboratory studies on individual components including fermented milk, yogurt, whey proteins, lactoferrin, α-lactalbumin, glycomacropeptide and immunoglobulin were comprehensively searched and retrieved from Medline, Embase, Scopus, Cochrane Controlled Trials Register and abstracts/ proceedings of conferences up to may 2013. The available studies/ meta-analysis were rated for quality as per the Scottish Intercollegiate Guidelines Network (SIGN) check lists[8] and the Quality Rating for Individual Studies[9]. The evidence was subsequently graded using the Revised Grading System[10]. The level of recommendation was later defined into one four grades (A, B, C or D; SIGN grades)[11].

# Fermented Milk

Fermented milk refers to whole or skimmed milk curdled to a beverage or custard like consistency by lactic acid producing bacteria. A wide assortment of products varying by the process, bacteria, duration and other variables are available and widely consumed in different countries. However, there are several commonalities. Fermented milk possesses a protein system constituted by two major families of proteins *i.e.* casein and whey proteins. Casein is insoluble, account for 80% of whole protein inventory. Whey proteins are globular water soluble molecules and include bovine lactoferrin, α-lactalbumin, glycomacropeptide, immunoglobulin, β-lactoglobulin and lactoperoxidase. Whey is contemplated to have the ability to act as an antioxidant, immune enhancer antihypertensive, antitumor, hypolipidemic, antiviral, antibacterial and as a chelating agent[12].

In the context of the helicobacter eradication there is a fair body of evidence from trials conducted using fermented milk (usual culturally/commercially available preparations including yogurt), fermented milk based probiotic preparations (FMPPs; fermented milk with specifically added live probiotic bacteria like lactobacilli) and capsule based probiotics. An observational study on 464 healthy Mexican subjects documented lower prevalence of *H. pylori* seropositivity in those consuming yogurt more than once a week compared with non-consumers[13]. As presented in Table 1, several clinical trials and a systematic review of RCTs compared an FMPP *vs* placebo or standard therapy plus FMPP *vs* standard therapy and documented a beneficial effect of FMPPs[14]. The overall quality and quantity of evidence for FMPPs appears convincing (Recommendation Grade-A) and beneficial effect appears to be sustained when FMPP were used in combination with standard therapy (Recommendation Grade A[15-18]). Also, benefit has been documented in symptomatic children (Recommendation Grade-B), symptomatic and asymptomatic adults (Recommendation Grade-B) and in patients failed eradication on standard therapy (Recommendation Grade-B). The overall magnitude of the benefit was estimated to be 5%-15%[14].

With reference to active principle responsible for this effect, the available clinical evidence can be better summarized on the basis of three arguments (Tables 1, 2 and 3). First, if whey proteins have clinically significant anti-helicobacter properties then FMPP alone or in combination with standard therapy should have documented effectiveness (improvement in eradication rates)[15-26]. Secondly, capsule based probiotic preparations (bacteria only) should be partly or completely ineffective in *H. pylori* eradication[27-38]. Thirdly, if FMPP’s are compared with a fermented milk control group then in the control group there should be some improvement partly or completely negating the effect of the addition of bacteria in the treatment group[39-41].

As summarized in Tables 1-3, the available evidence supports the above assertions and arguments. It is evident from the clinical studies and metaanalysis presented in Tables 1-3 that FMPPs have some efficacy against *Helicobacter* (10 positive trials and one positive metanalysis compared with 2 negative trials; Argument 1 above). It is also apparent from Table 1-3 that studies using capsule based probiotic preparations are predominantly negative (1 positive trial compared with 11 showing no benefit; and Argument 2). In support of Argument 3 the overall data on the beneficial effect of bacterial probiotic preparations in Helicobacter eradication can at best be classified as “equivocal” (3 trials with weak methodology and equivocal results). This apprehension is further substantiated by a meta-analytic sub-analysis presented in an earlier report[42]. In this sub-analysis the beneficial effect of these preparations was minimal and it failed on exclusion sensitivity analysis (exclusion of one study majorly altered results) in consonance with the hypothesized argument.

In the context of studies comparing FMPP with fermented milk, several results are noteworthy. Of the three trials reporting control group data, two (one RCT and one CCT; Evidence grade (1-)[39,40] documented an improvement in gastritis or C-UBT values in the control group which is consistent with argument presented earlier. In the third pre and post intervention trial (clinical trial, evidence grade 2[41]) no significant differences were observed during the period that yogurt was administered alone. Hence, although there are some discrepant results the preponderance of the available evidence appears consistent with the hypothesis that whey milk proteins may partly or completely explain the anti-helicobacter properties of fermented milk based probiotic preparations.

Overall, the recommendation for fermented milk may be classified as Recommendation Grade-A. The magnitude of the benefit achieved by FMPPs is small (-10%) but holds across a variety of preparations. FMPP’s also carry the potential inherent advantage of better patient acceptability. Thus, they could offer a viable alternative for complementing traditional regimens. Further research is necessary to identify the active substrate/s and to define the exact product to be used, the optimal clinical setting (prevention/treatment, first line therapy/recurrence, symptomatic/asymptomatic, gastritis/ulcer diseases, treatment failure *etc*) and potential benefits in the setting of high antibiotic resistance.

# Whey Proteins

Whey proteins are globular water soluble molecules constituting -20% of the milk protein system. The whey protein profile, including general chemical, physiochemical and biological properties is depicted in Table 4. β-LG comprises the maximum percentage of whey protein but it has not been documented to possess any anti-bacterial properties. Other proteins have promising antibacterial attributes and hence have been studied in *in vitro, in vivo* and in human trials. With specific reference to *H. pylori* infection and associated conditions lactoferrin, α-lactalbumin, glycomacropeptide and immunoglobulins appear to be potentially relevant and warrant further discussion.

***Bovine lactoferrin***

Bovine lactoferrin, an iron-binding glycoprotein, is a non-enzymatic antioxidant found in the whey fraction of fermented milk as well as in colostrum. The possibility that bLF may help to improve the *H. pylori* eradication rate was first conceived in 1997 when, in an *in vitro* study by Yamazaki et al, bLf was found to be bactericidal to *H. pylori* in brucella broth[43]. Later *in vitro* studies have confirmed the same and yielded evidence of the possible mechanism of bactericidal action of bLf relating it to the high iron-binding affinity and prevention of iron utilization by *H. pylori*[44,45]. An additional mechanism based on the interaction of bLf with the bacterial surface is also suggested in the context of bactericidal effect on S. mutans and V. Cholerae[46]. It has been observed that bLf can bind to the outer membrane of Gram-negative bacteria and trigger the release of lipopolysaccharides, and kill the bacteria through osmotic damage[47,48]. Building on the available evidence Wada *et al*[49] in their study examined the therapeutic effect of bLf on *H. pylori* infection using *in vitro* and *in vivo* experimental systems. In the experiment a significant inhibition of *H. pylori* binding to gastric epithelium was accomplished within 8 h after incubation. As a follow up experiment mice infected with *H. pylori* were given 10 mg of bLf orally every day and their stomachs were removed after 2 wk. 40.0% of all *H. pylori* attached themselves to the epithelium in the stomach of the non treated mice, whereas only 19.9% of the *H. pylori* did in the bLf-treated mice. However, in a similar experiment by Huynh *et al*[50], bLF, desferrioxamine and human recombinant lactoferrin had positive *in vitro* effects but all three failed to reduce *H. pylori* load in mice.

The above experimental evidence led to several human clinical trials. These are summarized in Table 5[43,51-57]. As presented the 5 (of 7 available) positive clinical trials and a meta-analysis appear to establish the beneficial effect of bLf (4%-17% as per meta-analysis) on *H. pylori* eradication fairly well[58]. The positive response was variously explained by the authors, 1) synergistic action of the antibiotics with bLf against *H. pylori*; 2) Inhibition of helicobacter growth in an acidic pH by bLf; 3) Ability of bLf to bind to iron inhibiting growth of *H. pylori*; and 4) decrease in incidence of side effects and non-compliance. Two studies by Zullo et al did not show any significant difference on addition of lactoferrin to triple therapy[56,57]. In the first study this could be explicable by the lack of synergism between lactoferrin and amoxicillin[56]. Alternatively, the anti-bacterial effect of lactoferrin based on bacterial membrane damage of Gram negative bacteria could be marginalized when amoxycillin is administered. In the second study the authors using quadruple therapy (rabeprazole, clarithromycin, tinidazole and lactoferrin) showed a statistically insignificant improvement in the eradication rate (4% in ITT analysis and 7% in per-protocol analysis). The results of this trial are limited by marked geographical heterogeneity (multicentric trial) in eradication rates.

Although the available evidence suggests that bLf is beneficial (Recommendation Grade-A), the magnitude of the documented benefit is small. Given that it lacks the inherent advantage in patient acceptability (requires to be given as a drug) that fermented milk potentially has the clinical significance of the benefit (other than suggesting that whey protein may be partly/completely responsible for the benefit with FMPP) remains unclear. Its role in various clinical settings and more so in the presence of high antibiotic resistance deserves further exploration.

***α-Lactalbumin***

α-Lactalbumin (α-LA) is a major milk protein comprising 20%-25% of whey proteins and has strong calcium binding ability. α-LA is reported to be biologically active *in vivo* with well-demonstrated antiulcer activity in rats. Matsumoto *et al*[59] in an *in vivo* study using ethanol ulcer model rats documented 82% reduction of ulcerative lesion index using 200mg/kg bw of α-LA. Similar results were reported by Mezzaroba *et al*[60], with absolute alcohol and indomethacin ulcer model rats given commercial α-LA. This intervention resulted in 30%-70% lower ulcerative lesion index in comparison with controls. The exact mechanism of the protective effect and its impact on Helicobacter is not well studied. However, as reported whey protein concentrates have consistently reported anti-helicobacter properties. The minimal evidence on the subject precludes any definitive comment on the potential of α-lactalbumin as an anti-helicobacter agent. The paucity of literature on the subject presents wide scope for future research.

***Glycomacropeptide***

Glycomacropeptide, (GMP) also referred to as caseinomacropeptide and caseinoglycopeptide, is formed when bovine κ-casein is hydrolysed into para-κ-casein which remains with the curd and GMP is removed with the whey. It constitute 15%-20% of whey protein. GMP has also been found to have several immunomodulatory functions and antibacterial properties. Otani *et al*[61] demonstrated that GMP which contains sialic acid inhibits the activity of Salmonella typhimurium lipopolysaccharide, inhibiting bacterial and viral adhesion especially to epithelial cells and dental plaque[62,63]. Other relevant properties like suppression of gastric secretions in dogs have been reported by a study group[64].

A study done in Japan attempted to enhance the ability of glycopeptides to bind pathogenic bacteria *in vivo* by conjugating with the non-digestible saccharides. The results of this study suggest that GMP could be a promising agent for preventing intestinal infection using its ability to bind pathogenic bacteria[65]. In the context of Helicobacter infection several authors have expressed the view that GMP has gastroprotective properties[66] but there is no direct evidence supporting its role in its eradication. Currently, in the absence of direct evidence the potential benefit of GMP in the treatment of *H. pylori* infection remains speculative.

***Immunoglobulins***

Immunoglobulins (IG) constitute a complex group, the elements of which are produced by B-lymphocytes. They make a significant contribution to the whey protein content (10%-15%). Some of them attach to surfaces, where they behave as receptors, whereas others function as antibodies, which are released in the blood and lymph. Early *et al*[67], in an *in vitro* study demonstrated that whey protein concentrates produced using milk from *H. pylori* immunized cows contains antibodies that are active at the pH of the stomach, and bactericidal against *H. pylori in vitro*. Oona *et al*[68] in their study on 20 children suffering from recurrent abdominal pain and with proven *H. pylori* infection showed alleviation of gastritis and/or a decrease in the degree of colonization of the antrum mucosa in nine children out of 14, and of the corpus mucosa in seven children out of 15 using immune colostrum of cows immunized (whole-cell vaccine prepared with *H. pylori* strain NCTC 11637) before calving. It is clear that evidence on the *in vivo* effects of the immunoglobulin in prevention or treatment of *H. pylori* infections in humans is only suggestive and deserves further work.

**Conclusion**

In conclusion, FMPP and bovine lactoferrin appear to be beneficial in helicobacter eradication (Evidence Grade-A or -B in various settings with level 1++ studies available)). Evidence for alpha-lactabumin and whey protein concentrates enriched in immunoglobulins is “suggestive of benefit”. However the studies are small and/or based on animals (Level 3 or 4 studies only; No Grading Possible). Literature on glycomacropeptide is very preliminary precluding relevant inferences. No studies directly comparing the efficacy of individual components amongst themselves or to FMPP were available. Overall, the magnitude of the potential benefit documented so far for the group is small and the precise clinical settings are poorly defined. This restricts more widespread use of this group as a complementary therapy in a nutraceutical setting hinging on better patient acceptability/compliance. Further work is necessary to identify the optimal substrate, fermentation process, dose of administration and the ideal clinical setting (prevention/treatment, first line therapy/recurrence, symptomatic/asymptomatic, gastritis/ulcer diseases *etc*). The potential of this group in a high antibiotic resistance or treatment failure settings presents interesting possibilities and deserves further exploration.

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**Table 1 Studies comparing “fermented milk based probiotic preparation” with placebo or “standard therapy + fermented milk based probiotic preparation” with “standard therapy”**

| **Ref.** | **Type of trial** | **Evidence grade1** | **Quality rating**2 | **Subjects** | **Study design** | **Study groups/ methods** | **Outcome variable/s** | **Results and conclusions** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Positive** | | | | | | | | |
| Bekar O *et al*[15], 2011, Turkey | Human | 1+ | + | 82 pts of dyspepsia and *H. pylori* infection | RCT | Two groups-Control group (*n* = 36; Triple therapy-lansoprazole, clarithromycin and amoxicillin+ placebo) and Treatment group (*n* = 46; Triple therapy+kefir (fermented milk drink containing probiotics)); given for 14 d | Eradication of *H. pylori*; adverse events of eradication therapy (Urease test after 45 d of treatment) | Significantly more patients (78.2% *vs* 50.0%) in the treatment group achieved eradication in comparison with control group. Side effects were less frequent and less severe in the treatment group. |
| Nagpal *et al*[14] 2009, India | Metaanalysis | 1+ | ++ | 10 eligible trials; data available for 963 patients. | Metaanalysis of human RCTs/CCTs | Trials had to be randomized or quasi-randomized and controlled, using a FMPP in the intervention group treating Helicobacter-infected patients. The only difference between the two groups had to be FMPP. | Eradication of *H. pylori*; adverse events of eradication therapy | The pooled odds ratio for eradication by ITT analysis in the treatment *vs* control group was 1.91 (1.38-2.67; *p* < 0.0001) using fixed effect model. The pooled risk difference was 0.10 (95%CI 0.05-0.15; *p* < 0.0001) by fixed effect model. Fermented milk based probiotic preparations improve *H. pylori* eradication rates by approximately 5-15%, whereas the effect on adverse effects is heterogeneous. |
| Sykora *et al*[16], 2005, Czech Republic and United Kingdom | Human | 1+ | ++ | 86 symptomatic *H. pylori* positive children | RCT | Two groups- OAC-LC group- Omeprazole, amoxicillin and clarithromycin for 7 d with fermented milk containing L.casei DN-114001 for 14 d (*n* = 39) *vs* OAC group- Omeprazole, amoxicillin and clarithromycin for 7 d (*n* = 47) | Eradication of *H. pylori*, Endoscopic and Histologic comparison | ITT based eradication rates for the group A were 84.6% and 91.6% by PP analysis. Eradication in the group B was 57.5% in the ITT and 61.3% in the PP group. Eradication success was higher in the group A compared to group B in both ITT (*P* = 0.0045) and PP analysis (*P* = 0.0019). |
| Sheu *et al*[17], 2006, Taiwan | Human | 1+ | + | 138 patients in whom triple therapy failed | RCT | Two groups-yogurt (containing L. acidophilus La5, Lactobacillus bulgaricus, Bifidobacterium lactis Bb12 and Streptococcus thermophilus)-plus-quadruple therapy group for 7 d (*n* = 69) *vs* quadruple therapy only group (*n* = 69) for 7 d | Successful eradication of *H. pylori*, drug compliance, side effects. | The yogurt-plus-quadruple therapy group had a higher *H. pylori* eradication rate than did the quadruple therapy only group (ITT analysis 85% *vs* 71.1%, *p* < 0.05; PP analysis- 90.8% *vs* 76.6%, *p* < 0.05). Side effects were more frequent in the quadruple therapy-only group than in the yogurt-plus-quadruple therapy group. |
| Miki *et al*[20], 2007, Japan | Human | 1- | ++ | 69 subjects who were positive for *H. pylori* infection | RCT | Two groups- Fermented milk (Bifidobacterium bifidum YIT) (BF-1) (*n* = 34) *vs* placebo (untreated milk) (*n* = 35) for 12 wk | Suppressive effect of BF-1 fermented milk on *H. pylori* urease activity and gastric situation | *H. pylori* infection was judged by the C-UBT. *H. pylori*-negativity (below 5%: *n* = 6 and 4 in the BF-1 and placebo groups, respectively) subjects. |
| Sheu *et al*[18], 2002, Taiwan | Human | 1- | + | 160 *H. pylori* infected patients | CCT | Two groups- triple plus yogurt (TYG) (containing L. acidophilus La5, Lactobacillus bulgaricus, Bifidobacterium lactis Bb12 and Streptococcus thermophilus) group (*n* = 80) *vs* triple only group (TG) (*n* = 80) for 7 d. | Successful eradication of *H. pylori*, drug compliance, side effects | By ITT analysis, the triple-plus-yogurt group had a higher *H. pylori* eradication rate than the triple-only group (*p* < 0.05) and side effects were more commonly found in the TG than in the TYG. Also a significantly higher proportion of patients in the TYG completed the 7-d regimen than in the TG (67.5% *vs* 43.8%, *P* < 0.05) |
| Felley *et al*[21], 2001, Boston | Human | 1- | + | 53 volunteers infected with *H. pylori* | CCT | Two groups-Acidified milk containing L. johnsonii La1(LC-1) (*n* = 25) *vs* Placebo (pasteurized milk) (*n* = 27) for 3 wk followed by 500 mg bid clarithromycin received by all subjects during the last two weeks. | Effect of the given treatment on *H. pylori* density, gastric inflammation and activity | In the LC-1 group, four had higher scores in the antrum, 14 were found to have a decreased *H. pylori* density reflected by lower scores (*p* = 0.02) and in the placebo group in antrum scores remain identical in 10 volunteers and decreased in 11 (0.08). The results suggest that *H. pylori* infection and gastritis can be down-regulated by LC-1 |
| Cats *et al*[22], 2003, Netherlands | Human | 1- | - | 14 *H. pylori* positive subjects | CCT | Two groups- Fermented milk (L.casei) for 3 wk (*n* = 14) *vs* control group (*n* = 6) | Effect of L.casei on urease activity *in vivo* (*H. pylori* positive subjects) | Urease activity decreased in nine of the 14 (64%) subjects with L. casei supplementation and in two of the six (33%) controls (*P* = 0.22). A slight, but non-significant, trend towards a suppressive effect of L. casei on *H. pylori* *in vivo* may exist. |
| Wang *et al*[19], 2004, Taiwan | Human | 1- | - | 70 volunteers infected with *H. pylori* | CCT | Two groups- AB yogurt (containing L. acidophilus La5, Lactobacillus bulgaricus, Bifidobacterium lactis Bb12 and Streptococcus thermophilus) (*n* = 59) *vs* milk placebo (*n* = 11) for 6 wk. | Effect of yogurt on *H. pylori* infection in humans | Administration of AB-yogurt decreased the urease activity of *H. pylori* after 6 wk of therapy (*p* < 0.0001). Regular intake of yogurt containing Bb12 and La5 effectively suppressed *H. pylori* infections in humans |
| Park *et al*, 2001, South Korea[23] | Human | NR | - | 40 *H. pylori* infected volunteers | CCT | Two groups- Fermented milk (Lactobacillus acidophilus, Lactobacilus casei) (*n* = 21) *vs* Placebo (*n* = 19) for 4 wk. | Eradication of *H. pylori*, Comparison of endoscopic findings, Compliance | All patients were compliant and the *H. pylori* density of antrum tended to decrease in treatment group compared with placebo group (*p* = 0.072). 3 cases in treatment group were noted for negative conversions of both rapid urease test and C-UBT. |
| Kim *et al*[24], 2007, South Korea | Human | FTNA | FTNA | 262 *H. pylori* infected patients | CCT | Two groups- triple plus yogurt group for 3 wk (*n* = 147) *vs* triple only group (*n* = 115) for 1 wk | Eradication of *H. pylori* | In PP analysis, *H. pylori* eradication rate in the yogurt group, 87.7% was marginally higher than that in control group, 78.4% (*p* = 0.055). And according to ITT analysis, the eradication rate in the yogurt group, 78.2% was also marginally higher than that of control group, 69.5% (*p* = 0.062) |
| **Negative** | | | | | | | | |
| Goldman *et al*[25], 2006, Argentina | Human | 1+ | ++ | 65 children who tested positive for *H. pylori* | RCT | Two groups- triple therapy with probiotic food (commercial yogurt containing Bifidobacterium animalis and Lactobacillus casei) (*n* = 33) *vs* triple therapy with placebo (milk fluid) (*n* = 32) | Eradication of *H. pylori* | We found no significant differences in *H. pylori* eradication rates at 1 and 3 mo between the treated group (ER 45.5% and 42.4%) and the control group (ER = 37.5% and 40.6%). Study could not demonstrate an adjuvant effect of the studied probiotic food to triple therapy in the eradication of *H. pylori* infection in children. |
| Song *et al*[26], 2005, South Korea | Human | NA | - | 70 patients with duodenal ulcer | CCT | Two groups- triple-plus-fermented milk (Lactobacilli) (*n* = 35) *vs* triple plus placebo (*n* = 35) | *H. pylori* eradication rate, Fermented milk group reduces treatment-related adverse reactions. | Eradication was successful in 88.6% in the Lactobacilli group and 85.7% in the placebo group (*p* = 1.00). Lactobacillus containing fermented milk couldn’t exert beneficial effects on *H. pylori* eradication or treatment-related adverse reactions. |

1Levels of evidence: 1++ High quality meta-analysis, systematic reviews of RCTs, or RCTs with a very low risk of bias; 1+ Well conducted meta-analysis, systematic reviews of RCTs or RCTs with a low risk of bias; 1- Meta-analysis, systematic reviews or RCTs or RCTs with a high risk of bias; 2++ High quality systematic reviews of case-control or cohort studies orhigh quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal; 2+ well conducted case control or cohort studoes with a low risk of confounding, bias, or chance and a significant risk that the relationship is not causal; 3 Non-analytic studies, *e.g.,* case reports, case series; 4 Expert opinion. 2Quality rating for individual studies: ++ Applies if all or most criteria from the checklist are fulfilled; where criteria are not fulfilled the conclusions of the study or review are thought very unlikely to alter; + Applies if some of the criteria from the checklist are fulfilled; where criteria are not fulfilled or are not adequately described, the conclusions of the study or review are thought unlikely to alter; - Applies if few or no criteria from the checklist are fulfilled; where criteria are not fulfilled or are not adequately described, the conclusions of the study or review are thought likely or very likely to alter. *H. pylori*: *Helicobacter pylori;* RCT: Randomised controlled trial; CCT: Controlled clinical trial; CT: Clinical trial; C-UBT: 13C-urea breath test; FMPP: Fermented milk based probiotic preparation; NR: Not reported; FTNA: Full text not available; NS: Not significant.

**Table 2 Studies comparing capsule based probiotic (bacteria only) with placebo or standard therapy plus capsule based probiotic *vs* standard therapy**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Type of trial** | **Evidence grade1** | **Quality rating**2 | **Subjects** | **Study design** | **Study groups/ methods** | **Outcome variable/s** | **Results and conclusions** |
| **Positive** | | | | | | | | |
| Canducci *et al*[27], Italy, 2000 | Human | 1 + | + | 120 *H. pylori* positive patients | RCT | Two groups: RCA (Rabeprazole, Clarithromycin, Amoxycillin) group- triple therapy (*n* = 60), RCAL group- triple therapy with Lactéol Fort for 7 d. | Effect of L. acidophilus could improve the efficacy of a standard anti-*H. pylori* therapy. | In RCA group eradication was successful in 72% at PP analysis or 70% at ITT analysis and in RCAL group eradication was achieved with 88% with PP analysis, 87% with ITT analysis. |
| **Negative** | | | | | | | | |
| Gotteland *et al*[28], 2005 | Human | 1 + | + | 254 children positive for *H. pylori* | RCT | Three groups: Antibiotics (group Ab)- (*n* = 57) for 8 d  , Lactobacillus acidophilus LB (group Ab)- (*n* = 63) for 8 wk, Saccharomyces boulardii plus inulin (group Sb1)- (*n* = 62) 8 wk | To evaluate the capacity of Lactobacillus acidophilus LB and of symbiotic combination of Sb plus inulin to interfere with *H. pylori* colonization in children | *H. pylori* was eradicated in 66%, 12% and 6.5% of the children from the Ab, Sb1 and LB groups, respectively. A moderate but significant difference in ∆ DOB was detected in children receiving living Sb1, but not in those receiving LB |
| Lionetti *et al*[29], 2006, Italy | Human | 1+ | ++ | 40 *H. pylori* positive children | RCT | Two groups: Group A- 10 d sequential therapy plus L. reuteri ATCC 55730, Group B-Placebo with the same therapy | Effect of Lactobacillus reuteri to prevent or minimize the gastrointestinal side-effects | No significant differences were observed between the groups in the success of *H. pylori* eradication. Treatment was successful in 17 of 20 [85% (95%CI: 68–100)] patients in probiotic supplemented when compared with 16 of 20 patients in placebo group [80% (95%CI: 61–99)] (*P* = NS). |
| Nista *et al*[30], 2004, Italy | Human | 1+ | ++ | 106 *H. pylori* positive patients | RCT | Two groups: Group A- triple therapy for 7 d plus Bacillus clausii (probiotic) for 14 d starting from the first day of the treatment (*n* = 54) Group B- triple therapy plus placebo (*n* = 52) | Effect of probiotic on incidence and severity of antibiotic-associated side-effects during anti- *H. pylori* therapy and eradication was evaluated with means of 13C-urea breath test. | The *H. pylori* eradication rate was similar between B. clausii and placebo groups. In particular, ITT analysis has shown *H. pylori* was eradicated in 39 of 54 patients (72.2%) in the B. clausii group and in 37 of 52 patients (71.15%) in the placebo group. In PP population, *H. pylori* was eradicated in 39 of 50 patients (78%) in the B. clausii group and in 37 of 50 patients (74%) in  the placebo group. |
| Cindoruk *et al*[32], 2007, Turkey | Human | 1+ | + | 124 patients with *H. pylori* infection | RCT | Two groups: Group A- triple therapy plus S. boulardii, Group B- triple therapy plus placebo for 14 d | Efficacy and safety of S. boulardii in the prevention of side effects and the eradication success of anti-*H. pylori* therapy. | *H. pylori* eradication rate, although higher in the treatment group, was statistically similar in treatment and control groups: 71% (44/62) verses 59.7% (37/62), respectively (*p* > 0.05). |
| Myllyluoma *et al*[32], 2005, Finland | Human | 1+ | + | 47 subjects with *H. pylori* infection | CCT | Two groups: Group A –probiotic drink (*n* = 23), group B- Placebo (*n* = 24) during *H. pylori* eradication and for 3 wk following the treatment. | Effect of probiotic therapy on symptoms associated with the recommended *H. pylori* eradication treatment. As a secondary end-point to find out whether this therapy could improve the eradication rate. | The *H. pylori* eradication rate was non-significantly higher in the group receiving probiotic therapy (91% *vs* 79%, *P* = 0.42). |
| Armuzzi *et al*[33], 2001, Italy | Human | 1+ | + | 60 healthy asymptomatic subjects screened positive for *H. pylori* infection | CCT | Two groups: Group A- triple therapy for 7 d plus Lactobacillus GG for 14 d during and the week after eradication therapy, Group B- triple therapy plus placebo | Effect of probiotic Lactobacillus GG to minimize or to prevent the occurrence of gastrointestinal side effects. | Helicobacter pylori eradication rates in group A was 83.33% (25/30) and in group B was 80% (24/30). *H. pylori* eradication rate had no significant difference. |
| Guo *et al*[34], China, 2004 | Human | FT NA | FT NA | 97 *H. pylori* positive symptomatic patients | CCT | Two groups: treatment group (triple therapy plus Bifid triple viable capsule containing Bifidobacteria longum, faecal streptococci, Lactobacillus acidophilus) (*n* = 47) control group: triple therapy (*n* = 50) | Efficacy of probiotic in the treatment of *H. pylori*. | Eradication rate was 93.6% (44/47) in treatment group and 88% in control group (44/50). *H. Pylori* eradication rate had no significant difference. |
| Armuzzi *et al*[35], 2001, Italy | Human | FT NA | FT NA | 120 healthy asymptomatic subjects screened positive for *H. pylori* infection | CCT | Two groups: Group A- triple therapy for 7 d plus Lactobacillus GG for 14 d during and the week after eradication therapy, Group B- triple therapy plus placebo | Effect of probiotic Lactobacillus GG to minimize or to prevent the occurrence of gastrointestinal side effects. | Helicobacter pylori eradication rates in group A was 80% (48/60) and in group B was 76.67% (46/60). *H. pylori* eradication rate had no significant difference. |
| Cremonini *et al*[36], Italy, 2002 | Human | FT NA | FT NA | 85 *H. pylori* positive, asymptomatic patients | CCT | Four groups- received both during and for 7 d after a 1 wk-triple therapy Group I- Lactobacillus GG (*n* = 21), group II-Saccharomyces boulardii (*n* = 22), group III-lactobacillus spp. And biphidobacteria (*n* = 21), group IV-placebo (*n* = 21) | Efficacy of probiotic in the eradication of *H. pylori* infection. | The *H. pylori* eradication rate was almost identical between the probiotic and placebo groups. |
| Tursi *et al*[37], 2004, Italy | Human | FT NA | FT NA | 70 patients with persistent *H. pylori* infection | CCT | Two groups- group A- quadruple therapy plus bacteria lactobacillus casei subsp. casei DG or group B- quadruple therapy only | Effect of probiotic supplementation on the effectiveness and tolerability of a new second-line 10 d quadruple therapy | *H. pylori* was negative in 33/34 group A patients (PP: 97.05% ITT: 94.28%) and 30/32 Group B patients. |
| Cao *et al*[38], China, 2005 | Human | FT NA | FT NA | 128 *H. pylori* positive symptomatic patients | CCT | Two groups: Group A -quadruple therapy plus Clostridium butyricum group B- quadruple therapy | Effect of treatment given in eradication of *H. pylori* | Eradication rates in group A 96.88% (62/64) and group B 92.19% (59/64) was not significantly different. |

1Levels of evidence: 1++ High quality meta-analysis, systematic reviews of RCTs, or RCTs with a very low risk of bias; 1+ Well conducted meta-analysis, systematic reviews of RCTs or RCTs with a low risk of bias; 1- Meta-analysis, systematic reviews or RCTs or RCTs with a high risk of bias; 2++ High quality systematic reviews of case-control or cohort studies orhigh quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal; 2+ well conducted case control or cohort studoes with a low risk of confounding, bias, or chance and a significant risk that the relationship is not causal; 3 Non-analytic studies, *e.g.,* case reports, case series; 4 Expert opinion. 2Quality rating for individual studies: ++ Applies if all or most criteria from the checklist are fulfilled; where criteria are not fulfilled the conclusions of the study or review are thought very unlikely to alter; + Applies if some of the criteria from the checklist are fulfilled; where criteria are not fulfilled or are not adequately described, the conclusions of the study or review are thought unlikely to alter; - Applies if few or no criteria from the checklist are fulfilled; where criteria are not fulfilled or are not adequately described, the conclusions of the study or review are thought likely or very likely to alter. *H. pylori*: *Helicobacter pylori;* RCT: Randomised controlled trial; CCT: Controlled clinical trial; CT: Clinical trial; NR: Not reported; NS: Not significant.

**Table 3 Clinical trials comparing** **fermented milk based probiotic preparations *vs* plain fermented milk**

| **Ref.** | **Type of trial** | **Evidence grade1** | **Quality rating**2 | **Subjects** | **Study design** | **Study groups/ methods** | **Outcome variable/s** | **Results and conclusions** | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Positive** | | | | | | | | | |
| Pantoflickova *et al*[39], 2003, Switzerland | Human | 1- | ++ | 50 *H. pylori* positive healthy volunteers | RCT | Two groups- fermented milk with LC (*n* = 25) *vs* fermented milk as Placebo (*n* = 25). Subjects took the treatment twice daily during the first 3 wk and once daily for the next 13 wk. | Effect of LC1 intake without antibiotics on *H. pylori* gastritis, *H. pylori* density | LC1 intake had a favorable, albeit weak, effect on *H. pylori* associated gastritis, particularly in the antrum. Regular ingestion of fermented milk containing L.johnsonii may reduce the risk of developing disorders associated with high degrees of gastric inflammation and mucus depletion | Placebo intake led to a decrease in severity and activity of gastritis in the antrum (inflammatory cell score after 3-wk and 16 wk consumption: 6.3 ± 0.7 and 6.4 ± 1.0, respectively).In the placebo group, mucus depletion scores remained at the same level during the whole duration of the study. *H. pylori* density decreased in 38% of subjects after 3 wk and 50% after 16 wk. |
| Horie *et al*[40], 2004, Japan, South Korea, Egypt | Human | 1- | - | 42 subjects with *H. pylori* infection | CCT | Two groups- A- test group (yogurt containing 1,5 g of egg yolk IgY-urease 3 times daily) (*n* = 22), B- control group (IgY-urease free yogurt) (*n* = 20) | Effect of IgY-Urease drinking yogurt on C-UBT values | TG showed a reduction in UBT values from 51.18 ± 3.40 at wk 0 to 33.70 ± 3.50 and 31.03 ± 3.54 at 2 and 4 wk resp. Suppression of *H. pylori* infection in humans could be achieved by consumption of drinking yogurt fortified with IgY-urease | CG showed some decrease in UBT values from 51.40 ± 4.48, to 44.38 ± 5.17 and 43.53 ± 5.48 at 0, 2 and 4 wk, resp. There was no significant difference obtained at week 0 and weeks 2 or 4. |
| Sakamoto *et al*[41], 2001, Japan | Human | 2- |  | 31 subjects infected with *H. pylori* infection | CT | The study was conducted in two parts. 1st part = 90 g of yogurt (0-9 wk). 2nd part = 90 g yogurt containing LG21 (9-18 wk) | Efficacy of lactobacillus gasseri OLL2716 (LG21) as a probiotic for helicobacter pylori | The [13C ] urea breath test and assays of serum pepsinogens revealed a significant improvement following LG21 treatment. LG21 was thus determined to be effective in both suppressing *H. pylori* and reducing gastric mucosal inflammation. | There was no significant difference in C-UBT levels at 0 (26.2 ± 15.1) and 9 (26.6 ± 13.7) wk |

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**Table 4 Whey protein components and its basic properties**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Whey components** | **Concentration (g/l)** | **% of Whey Protein** | **Molecular weight (kDa)** | **Number of amino acids residues** | **Biological properties** | **Recommendation grade against *Helicobacter*1** |
| **β-Lactoglobulin** | 1.3 | 50%-55% | 18277 | 162 | Source of essential and branched chain amino acids | - |
| **α-Lactalbumin** | 1.2 | 20%-25% | 14175 | 123 | Primary protein found in human breast milk.  Source of essential and branched chain amino acids | D |
| **Immunoglobulins**  **(A, B and C)** | 0.7 | 10%-15% | 25000 (light chain) + 50000-70000 (heavy chain) | - | Primary protein found in colostrum Immune modulating benefits | D |
| **Lactoferrin** | 0.1 | 1%-2% | 80000 | 700 | Antioxidant  Antibacterial, antiviral, and antifungal  Promotes growth of beneficial bacteria  Naturally occurs in breast milk, tears, saliva, bile, blood, and mucus | A |
| **Lactoperoxidase** | 0.03 | 0.50% | 70000 | 612 | Inhibits growth of bacteria | - |
| **Bovine Serum Albumin** | 0.4 | 5%-10% | 66267 | 582 | Source of essential amino acids  Large protein | - |
| **Glycomacropeptide** | 1.2 | 10%-15% | 6700 | 64 | Source of branched chain amino acids  Lacks the aromatic amino acids phenylalanine, tryptophan and tyrosine | D |

1Grades of recommendations: A: At least one meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population or A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1++ directly applicable to the target population and demonstrating overall consistency of results; B: A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results or Extrapolated evidence from studies rated as 1++ or 1+; C: A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results orExtrapolated evidence from studies rated as 2++; D Evidence level 3 or 4 orExtrapolated evidence from studies rated as 2+.

**Table 5 Studies comparing bovine lactoferrin with placebo or “standard therapy + bovine lactoferrin” with “standard therapy”**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Ref. | Type of Trial | Evidence grade**1** | Quality rating2 | Subjects | Study design | Study groups | Outcome variable | Results and conclusion |
| Nagpal *et al*[58], 2009, India | Metaanalysis | 1+ | ++ | 5 trials; 682 subjects [bLF group (*n* = 316); control group (*n* = 366)] | Metaanalysis of human RCTs/CCTs | Trials had to be randomized or quasi-randomized and controlled, using bLF in the intervention group treating Helicobacter-infected patients. The only difference between the two groups had to be bLF. | Eradication of *H. pylori*; adverse events of eradication therapy | The pooled odds ratio (5-studies) for eradication by intention to treat analysis was 2.22 (95%CI: 1.44-3.44; *p* = 0.0003) using the fixed effects model (FEM) and 2.24 (95%CI: 1.15-4.35; *p* = 0.0003) using the random effects model (REM) (Cochran’s Q = 6.83; *p* = 0.145). The pooled risk difference was 0.11 (95%CI: 0.05 -0.16; *p* = 0.0001) by FEM (Cochran’s Q = 6.67; *p* = 0.154) and 0.10 (95%CI: 0.04-0.17; *p* = 0.0023) by REM. There was no significant difference in incidence of adverse effects. |
| DI Mario *et al*[51], 2003, Italy | Human | 1+ | + | 150 consecutive  *H. pylori*-positive patients suffering from dyspeptic symptoms, gastritis and peptic ulcer disease. | RCT | Three groups – A-triple therapy (rabeprazole,clarithromycin,tinidazole) with lactoferrin for 7 d (*n* = 51), B-triple therapy for 7 d (*n* = 52), C- triple therapy for 10 d (*n* = 47). | Efficacy of standard triple therapy plus bovine lactoferrin in the eradication of *H. pylori* | Eradication rates (ITT) were A- 92.2%, B-71.2%, C-70.2 %. Results suggest that lactoferrin tested in the present study was effective in curing *H. pylori* and could be a new agent to assist the antimicrobials in the eradication of the bacterium. |
| Di Mario *et al*[52], 2006, Italy | Human | 1+ | + | 402 consecutive  *H. pylori*-positive patients suffering from dyspeptic symptoms, gastritis and peptic ulcer disease. | RCT | Three groups – A- triple therapy (esomeprazole,clarithromycin,tinidazole) for 7 d (*n* = 136), B-lactoferrin followed by triple therapy for 7 d (*n* = 132), C- triple therapy with lactoferrin (*n* = 134) | Efficacy of bovine lactoferrin in the treatment of *H. pylori* infection | Eradication rate (ITT)- A- 77%, B- 73%, C=90%. Incidence of side effects was A- 9.5%, B- 9%, C- 8.2%.  Results demonstrate that bovine lactoferrin is an effective adjuvant to triple therapy for eradication of *H. pylori* Infection. |
| Okuda M[53], 2005,  Japan | Human | 1- | + | 59 *H. pylori* infected healthy volunteers or children who were enrolled in a previous epidemiological study. | CCT | Two groups- bLF (*n* = 31), placebo (*n* = 28) | Efficacy of a single administration of bLF. Improvement of *H. pylori* infection, adverse effects. | Positive response (> 50% decrease in C-UBT values) was observed in 10 of 31 bLF-treated subjects and 1 of 28 control subjects, indicating that the rate of positive response in the bLF group was significantly higher than that in the control group. |
| Tursi A *et al*[54], 2007,  Italy | Human | 1- | + | 70 consecutive patients with persistent *H. pylori* infection after failure of a first standard treatment. | CCT | Two groups- A-quadruple therapy (ranitidine bismuth citrate plus triple therapy- esomeprazole ,amoxicillin, tinidazole) (*n* = 35), B- quadruple therapy plus lactoferrin (*n* = 35) | Efficacy and tolerability of bLF supplementation to this quadruple therapy in re-treating *H. pylori* infection. | Eradication rate- A-88.57%, B-94.28%. Side effects- A-29.41%, B-17.64%. bLF supplementation was found effective in reducing side-effect incidence. It seems capable of achieving a slight (NS statistically) improvement in eradicating *H. pylori*. |
| Zullo A *et al*[55], 2005,  Italy | Human | 1+ | ++ | 133 consecutive patients with non-ulcer dyspepsia and *H. pylori* infection. | RCT | Two groups- A- triple therapy for 7 d (*n* = 68), B- quadruple therapy (triple therapy plus lactoferrin) (*n* = 65) | Eradication rate of *H. pylori* infection, side effects and compliance. | Eradication rate (ITT) A- 77.9%, B- 76.9%. Side effects- A –10.3%, B- 9.2%. Quadruple therapy with bLF did not significantly increase the *H. pylori* cure rate of standard 7-d clarithromycin-amoxycillin based triple therapy in non-ulcer dyspepsia patients. |
| Zullo A *et al*[56], 2007,  Italy | Human | 1+ | + | 144 consecutive dyspeptic patients | RCT | Two groups – A- triple therapy (rabeprazole, levofoxacin, amoxycillin) (*n* = 72), B- quadruple therapy (rabeprazole, clarithromycin, tinidazole plus bovine lactoferrin) (*n* = 72) | Eradication rate of *H. pylori* infection, side effects and compliance. | Eradication rate (ITT) A- 68.1%, B-72.2%. *H. pylori* eradication rate following both quadruple therapy with lactoferrin and a low-dose PPI, triple therapy with levofloxacin is disappointingly low. |
| Imoto et al, 2004[57] | Human | FTNA | FTNA | 25 H. pylori positive healthy volunteers | CCT | Two groups- A- bLf mixed with a commercial yogurt (*n* = 16) B- yogurt (*n* = 9) | Effect of bLf against H. pylori | The C-UBT values at week 8 were significantly lower than those at week 0 in the bLf group (*p* < 0.01), whereas no difference was observed in the control group. |

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