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Fermented Products and their Potential Influences on Health and Disease

Gabriela Riscuta **MD**, CNS

Nutritional Science Research Group

National Cancer Institute
gabriela.riscuta@nih.gov

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

DISCLOSURE

- The information presented here is my personal opinion and does not represent National Cancer Institute official position.
- I have no actual or potential conflict of interest in relation to this presentation.

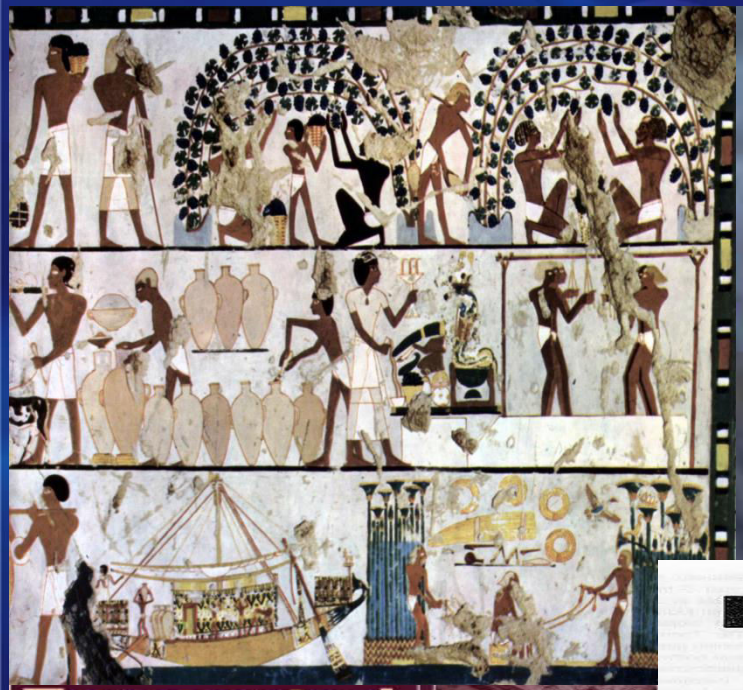
Historical Consumption of Fermented Foods



Humans consume fermented food since ancient times as a result of the natural fermentation process which precedes human history.

- **Controlled fermentation was used historically since 8000 BC to produce alcoholic beverage from fruits, rice, and honey.**
- **Fermentation processes involve the use of**
  - **yeast to produce alcohol from carbohydrates**
  - **bacteria such as lactobacillus , for producing yogurt , kefir, cheese and sauerkraut.**

- **The science of fermentation is known as zymology .**



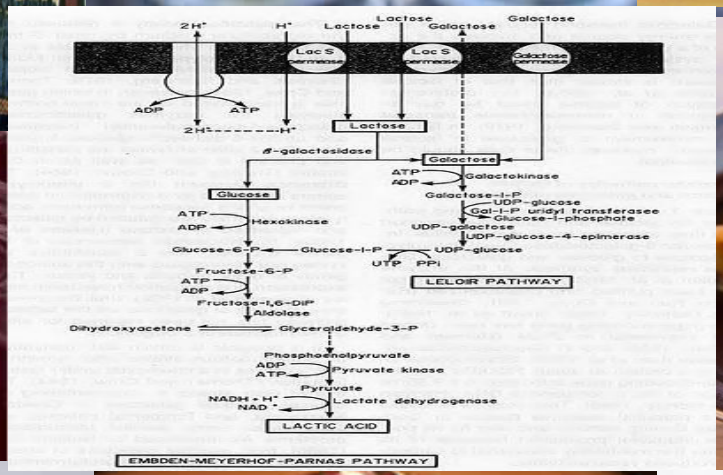




Fermented Meat and Poultry

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Historical Consumption of Fermented Dairy Products

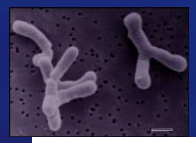
- Fermented milk products have been produced and consumed since around 10,000 BC.
- In the beginning of the 20th century, the Russian Nobel prize winner Élie Metchnikoff observed a high life expectancy in Bulgarian persons who ate large amounts of yogurt.
- Milk products/cultured dairy products, are mostly produced using **lactic acid bacteria** such as **Lactobacillus, Lactococcus , and Leuconostoc**.
- The fermentation process
  - increases the shelf-life of the product
  - enhances the taste
  - improves the digestibility of milk.
  - health benefits ?

Probiotics, Prebiotics and Synbiotics

- **The Probiotics** definition as originally framed by WHO/FAO is broadly accepted and as **" live microorganisms which, when administered in adequate amounts confer a health benefit on the host**.

- **Prebiotics** are "**non-viable food components that confer a health benefit on the host associated with modulation of the microbiota**". By definition, constitute a selective substrate for one or a limited number of beneficial bacteria and are able to alter the colonic microbiota in favor of a healthier composition.

- **Synbiotics:** the combination of probiotics and prebiotics.



Fermented Dairy Produced by Lactic Acid Bacteria

Product	Alternative names	Typical milkfat content	Typical shelf life at 4°C	Fermentation agent	Description
Cheese		1-75%	varies	a variety of bacteria and/or mold	Any number of solid fermented milk products.
Cultured buttermilk		1–2%	10 days[1]	Lactococcus lactis*[3] (Lactococcus lactis subsp. lactis*, Lactococcus lactis subsp. cremoris, Lactococcus lactis biovar. diacetylactis and Leuconostoc mesenteroides subsp. cremoris)[1]	Mesophilic fermented pasteurized milk
Acidophilus milk	acidophilus cultured milk	0.5-2%	2 weeks[1]	Lactobacillus acidophilus[1][3]	Thermophilic fermented milk, often lowfat (2%, 1.5%) or nonfat (0.5%), cultured with Lactobacillus acidophilus
Crème fraîche	creme fraiche	30-40%	10 days[1]	naturally occurring lactic acid bacteria in cream	Mesophilic fermented cream, originally from France; higher-fat variant of sour cream
Filmjölk	fil	0.1-4.5%	10–14 days[1]	Lactococcus lactis* and Leuconostoc[4][5]	Mesophilic fermented milk, originally from Scandinavia
Viili	filbunke	0.1-3.5%	14 days[1]	Lactococcus lactis subsp. cremoris, Lactococcus lactis* biovar. diacetylactis, Leuconostoc mesenteroides subsp. cremoris and Geotrichum candidum[6]	Mesophilic fermented milk that may or may not contain fungus on the surface; originally from Sweden; a Finnish specialty[6]
Kefir	kephir, kewra, talai, mudu kekiya, milkkefir, búlgaros	0-4%	10–14 days[1]	Kefir grains, a mixture of bacteria and yeasts	A fermented beverage, originally from the Caucasus region, made with kefir grains; can be made with any sugary liquid, such as milk from mammals, soy

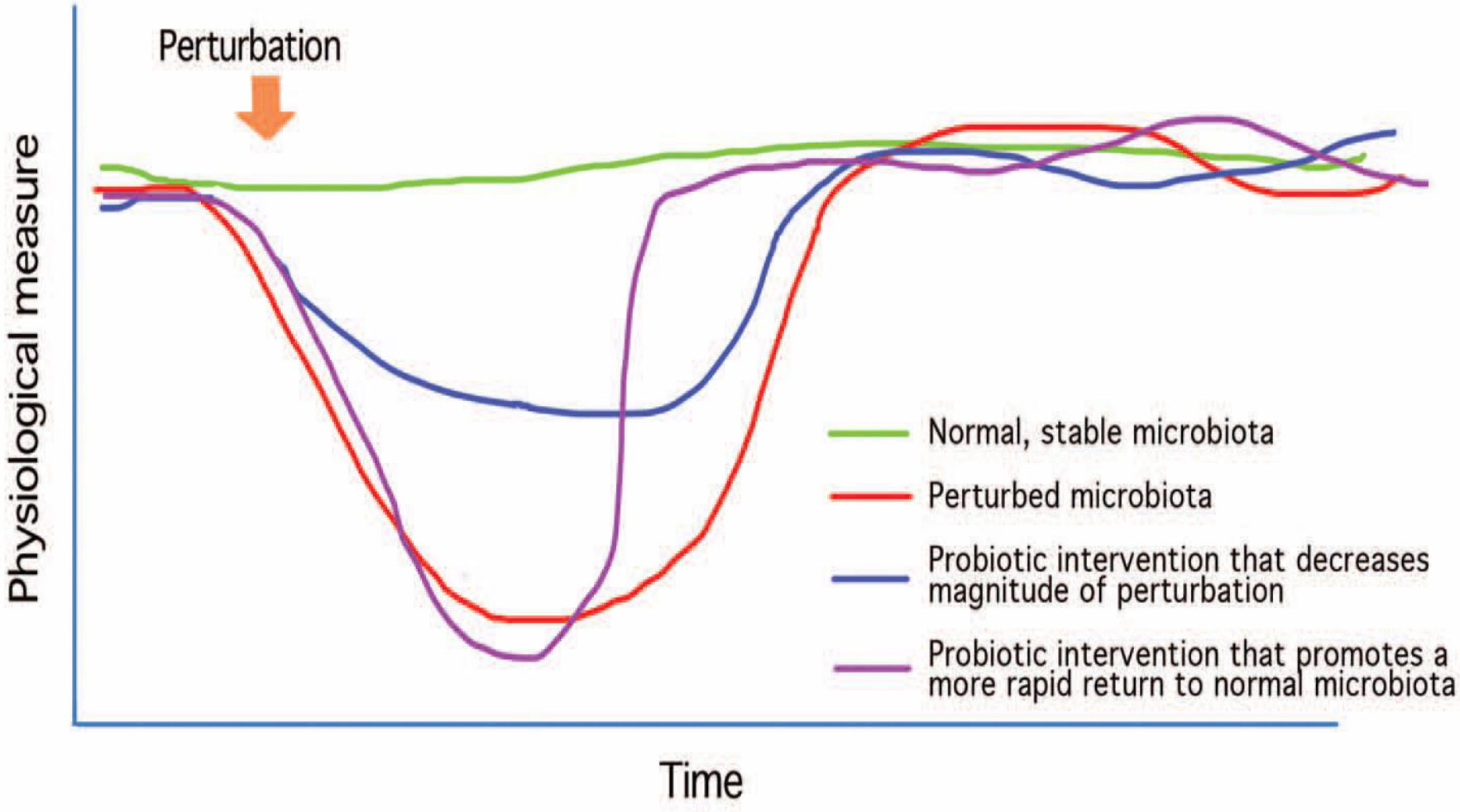
Lactic Acid Bacterial Strains and Their Anticancer Functions

Prevention	LAB strains	Functions
Apoptosis	*Lactobacillus acidophilus*	Anti-cancer cell growth and differentiation Direct induction of Beclin-1 and GRP78
	L. reuteri	Proliferation (Cox-2, cyclin D1) and cell survival (Bcl-2, Bcl-xL) Enhances MAPK activities including c-Jun N-terminal kinase and p38 MAPK
	L. acidophilus and *L. rhamnosus*	Induce Beclin-1 and GRP78, as well as indirectly through the induction of Bcl-2 and Bak
	L. acidophilus and *L. casei*	5-fluorouracil apoptosis induction
Antioxidant DNA damage	*Bifidobacterium longum* and *L. acidophilus*	Antioxidative activity, inhibiting linoleic acid peroxidation
	Streptococcus thermophilus	Releasing ROS protective factors
Immune response improvement	*L. acidophilus*	Stimulates DCs to produce inflammatory cytokines IL-12 and regulatory IL-10
	LTA-deficient *L. acidophilus*	Induces IL-10 in DCs, down-regulates IL-12 levels Increases densities of effector $Foxp3^{+}ROR\gamma t^{-}$ Tregs
	L. acidophilus, L. casei and *B. longum*	Enhance the total numbers of T cells, NK cells, MHC class II+ cells, and CD4-CD8+ T cells
	L. casei Shirota (LcS)	Induces cytokines, such as IFN-γ, interleukin-β (IL-1β) and TNF-α
	B. adolescentis	Increases the production of TNF-α
Epigenetics	LTA-deficient *L. acidophilus*	Enhances the expression of tumor suppressor genes
New anticancerfunction	*Pediococcus pentosaceus* FP3 *L. salivarius* FP25 *L. salivarius* FP35 *Enterococcus faecium* FP51	Adhere to colon cancer cells and trigger bioproduction of SCFA

LAB: Lactic acid bacteria; LTA: Lipoteichoic acid; SCFA: Short-chain fatty acid; DC: Dendritic cell; NK: Natural killer; IL: Interleukin; TNF: Tumor necrosis factor.

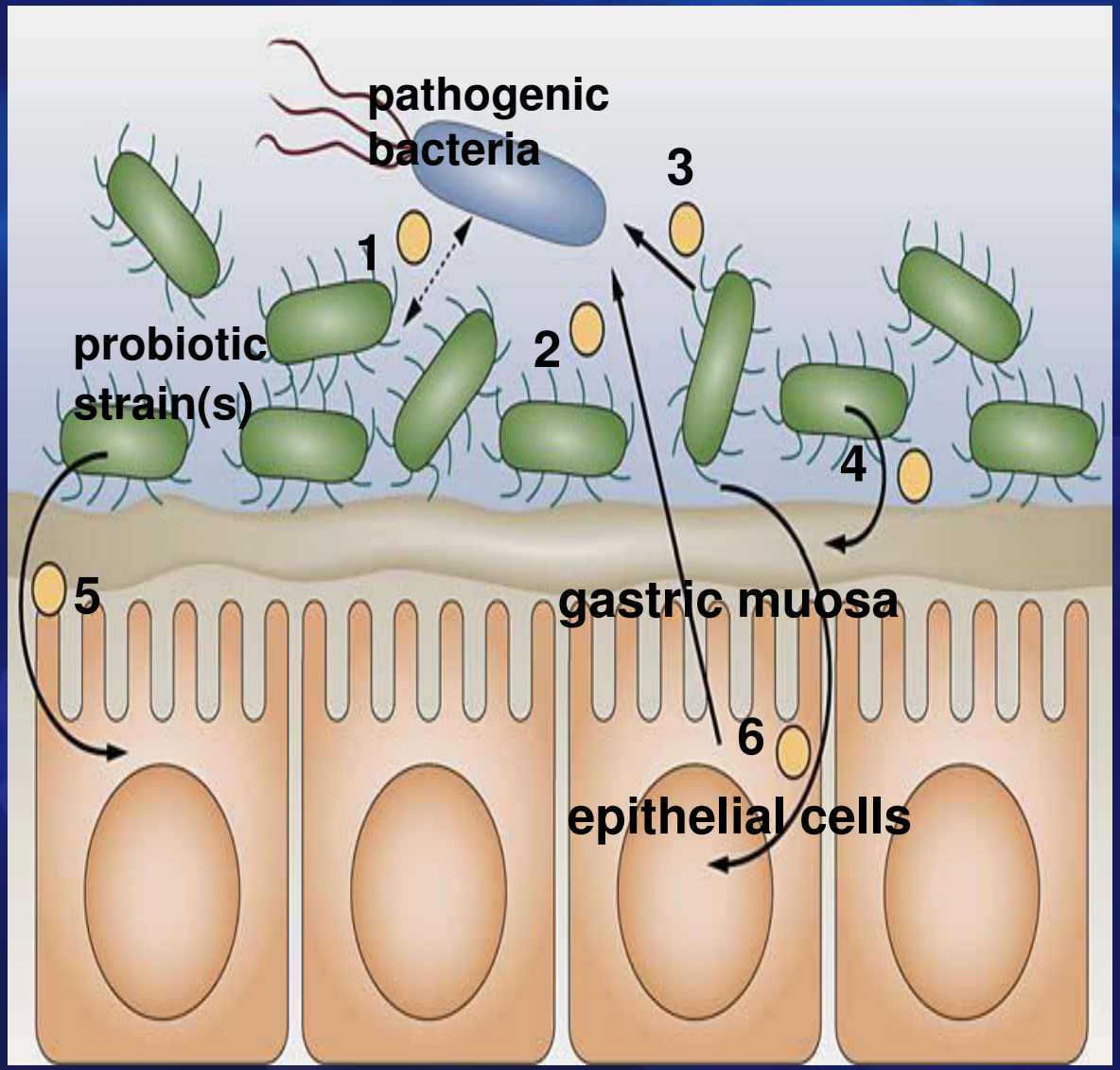
Li Zhong et. al World J Gastroenterol.2014

Probiotic Flora and Microbiome – Defining Health and Disease



Sanders, ME et al Gut Microbes 2011; 2:3 127

Mechanisms in Probiotic Interaction with Intestinal Epithelium



1.Competitive exclusion of pathogenic bacteria adhesion

2.Stimulation of a protective humoral immune response (production of IgA, IgG, IgM);

3 Antimicrobial activities, e.g. by decreasing pH, increasing bacteriocin or H 2 O 2);

4. Enhancing mucosal barrier integrity;

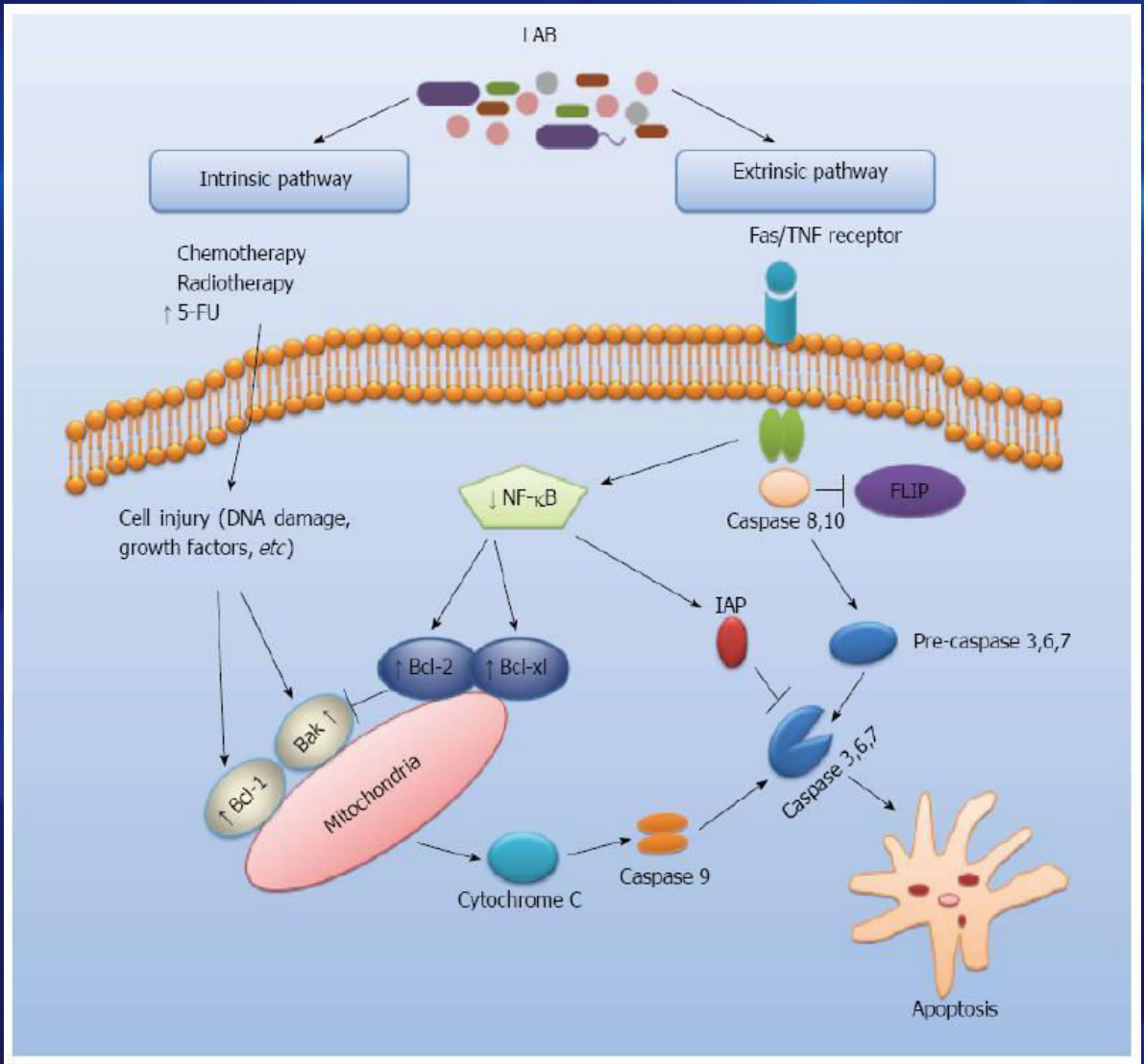
5 Release of polyamines (e.g. spermine, spermidine);

6. Inhibition of the inflammatory response (e.g. NF- B and MAP kinases).

Girardin M, Dig Dis 2011;29:574

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Potential Mechanisms of Action of Lactic Acid Bacteria via Extrinsec and Intrinsec Pathways of Apopotosis



Intrinsec pathway :

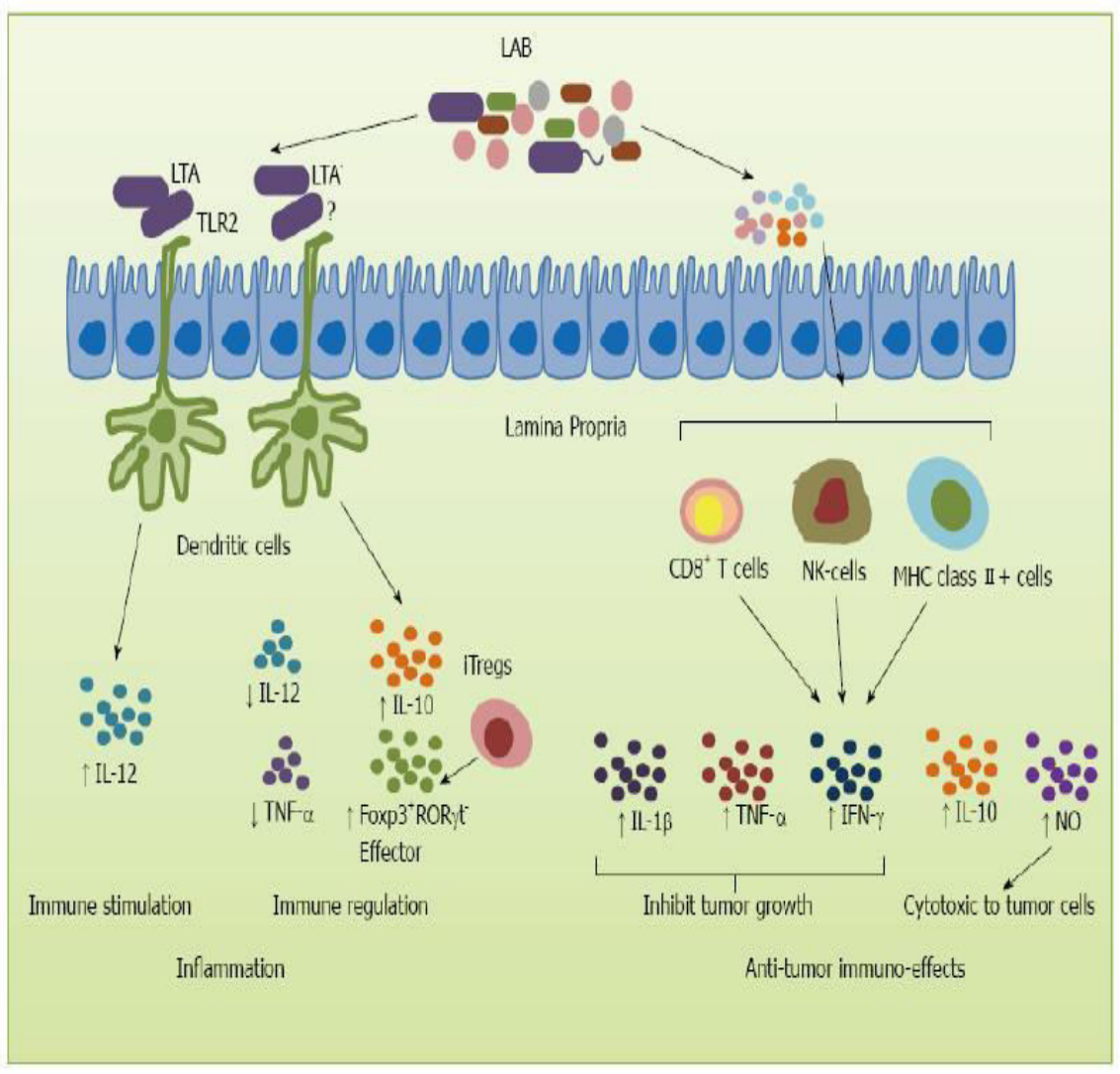
- LAB possibly enhances the apoptotic activity of 5-FU and it may induce the activation of autophagic cell death

Extrinsec pathway

- Engages FAS/tumor necrosis factor receptors to induce caspase related pathway.

Li Zhong et. al World J Gastroenterol.2014

Immune Responses Induced by Lactic Acid Bacteria (LAB)

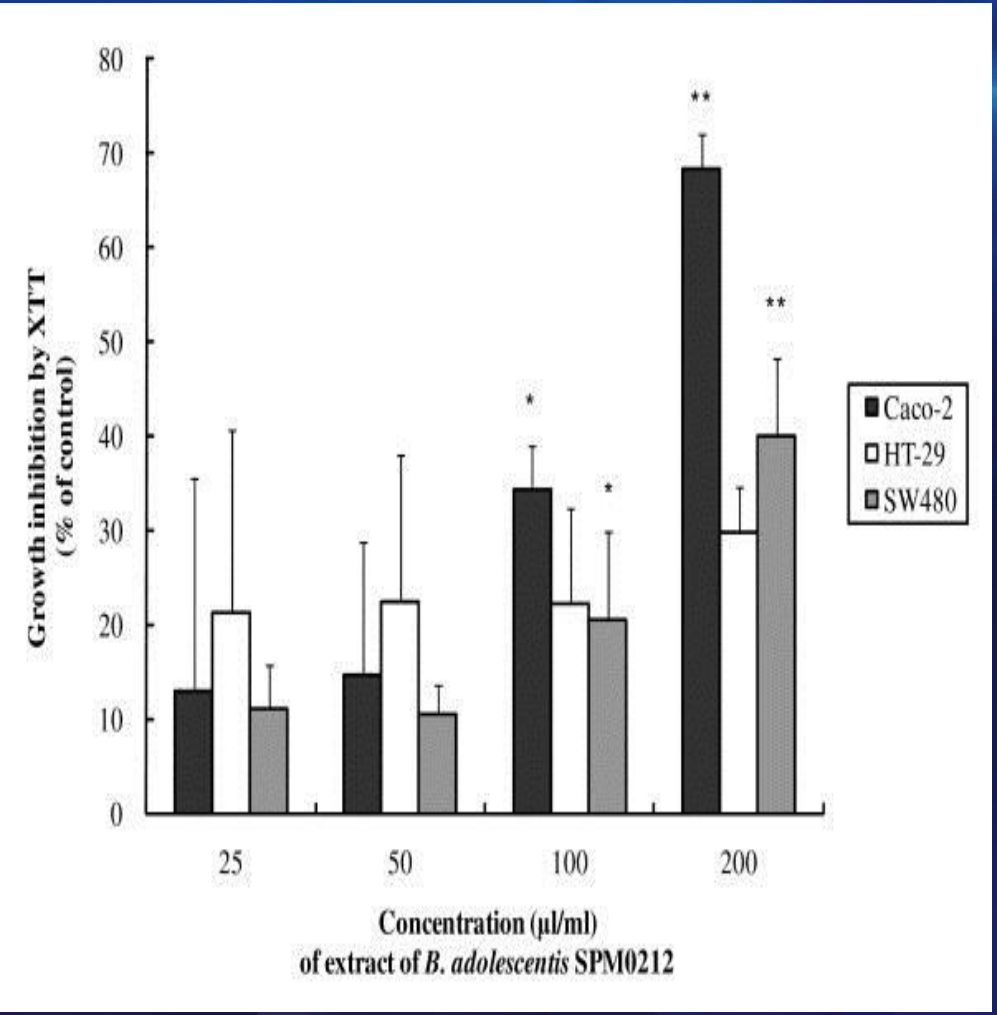


LAB may induce immune responses through two main pathways :

- Inflammation : involves lipotheicoic acid (LTA) and interleukin release;
- Anti-tumor immuno-effects : stimulate Tcells, dendritic cells and natural killer cells.

Li Zhong et. al World J Gastroenterol.2014

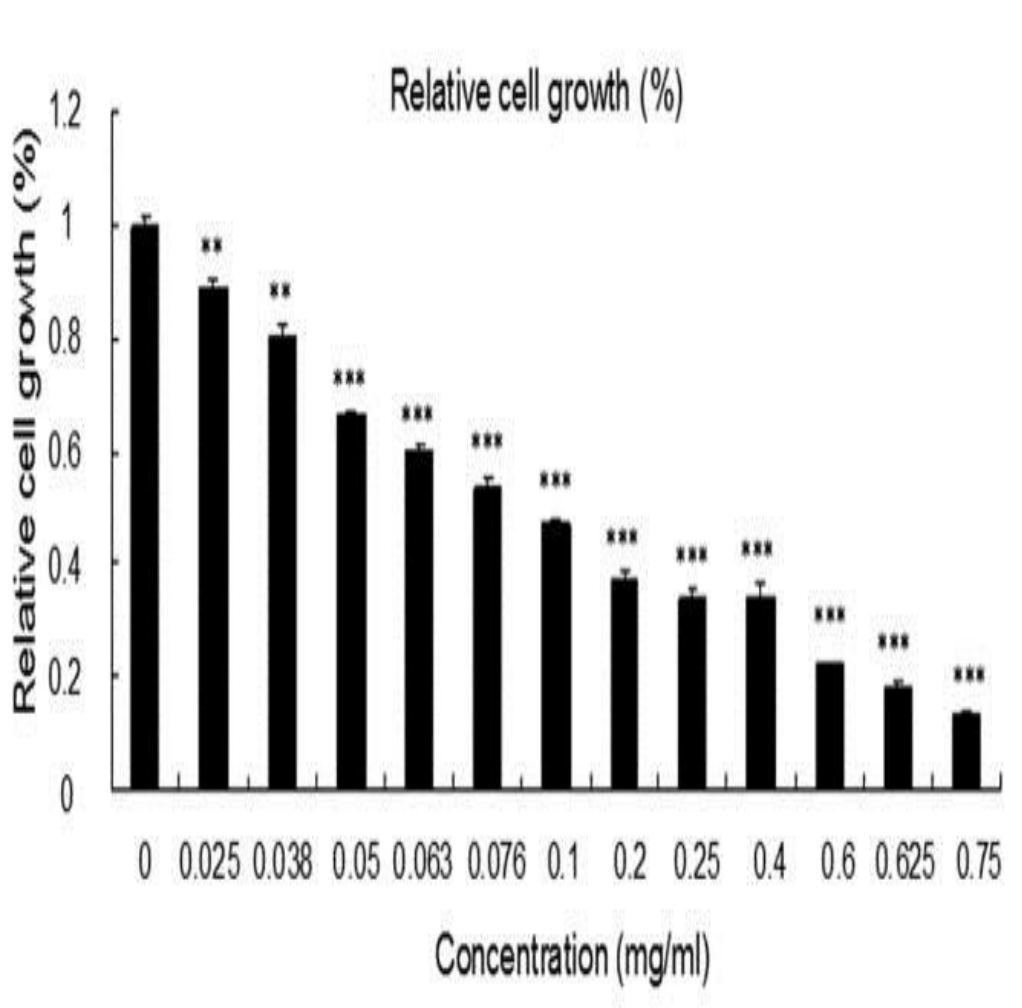
Effects of growth inhibition by *B. adolescentis* SPM0212 on colon cancer cell lines (Caco-2, HT-29 and SW480).



- The cells were treated with *B. adolescentis*
- The absorbance was measured using an ELISA reader at 490 nm.
- The quantitative data were presented as means ± SD of three independent experiments.
- Control versus treatment groups, $*p < 0.05$; $**p < 0.01$.

Do Kyung Lee et. al BMC Cancer. 2008;

Fermentation supernatants of *Lactobacillus delbrueckii* inhibit growth of human colon cancer cells and induces apoptosis



Effect of LBF solution on the proliferation of colon cancer SW620 cells.

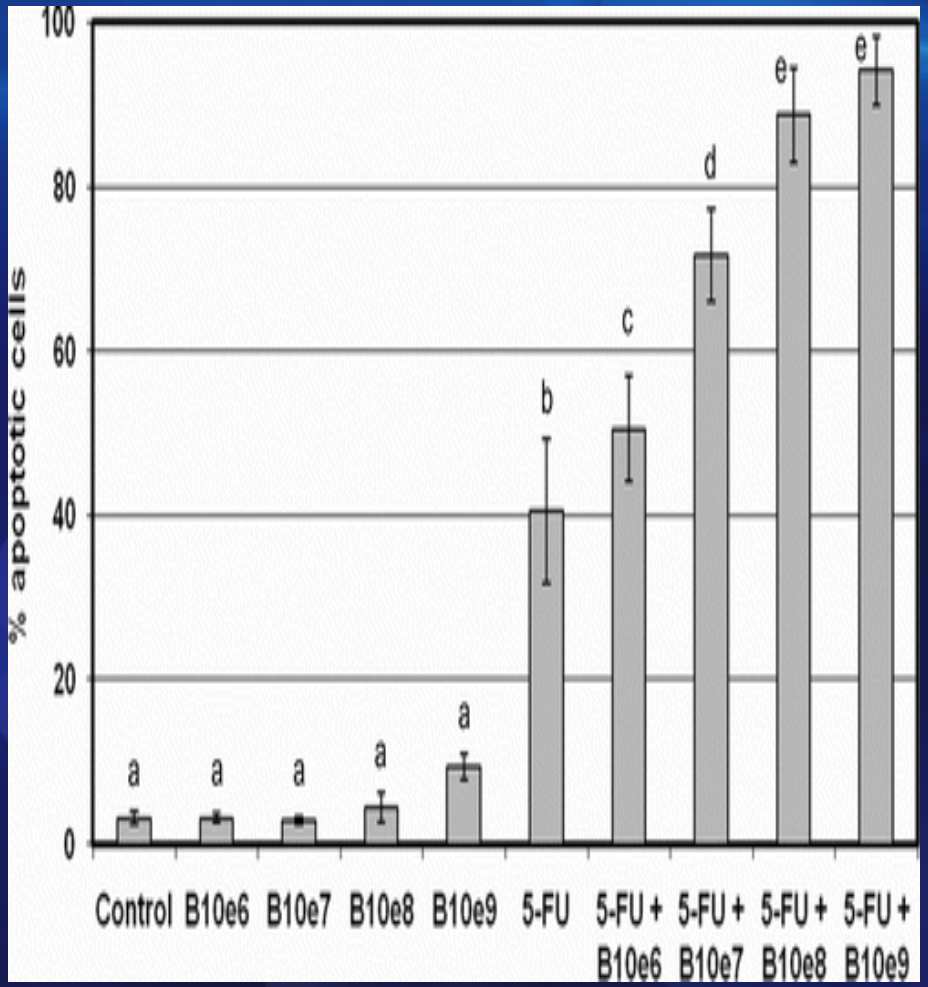
The SW620 cells were treated with various concentrations of LBF solution for 24 h. Growth is expressed as relative to untreated control cells.

Multiple comparison test was used for statistical analysis. $^{**}P<0.01$ and $^{***}P<0.001$, vs. untreated control cells. LBF, *Lactobacillus delbrueckii* fermentation

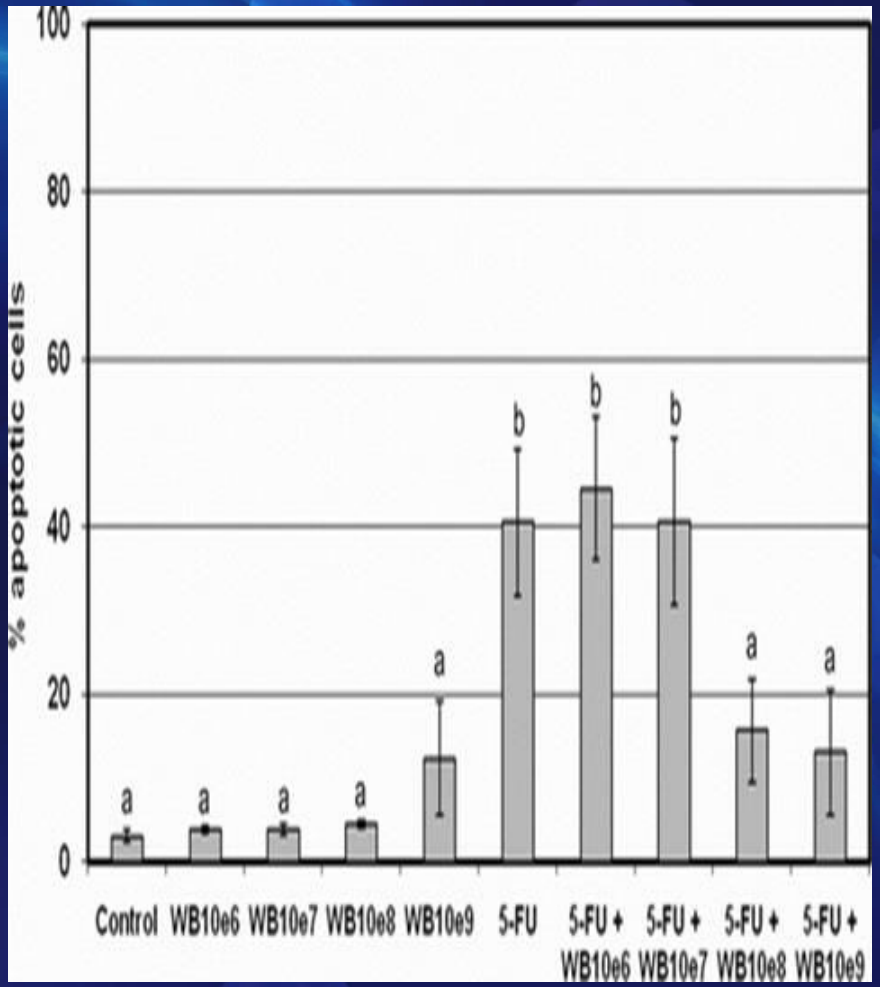
Wan Y 2014 Oncol Lett. May 2014

Effect of *L. Acidophilus* and *L. Casei* mix in the presence of 5-fluorouracil (5-FU) on LS513 cell apoptosis

Live Bacteria



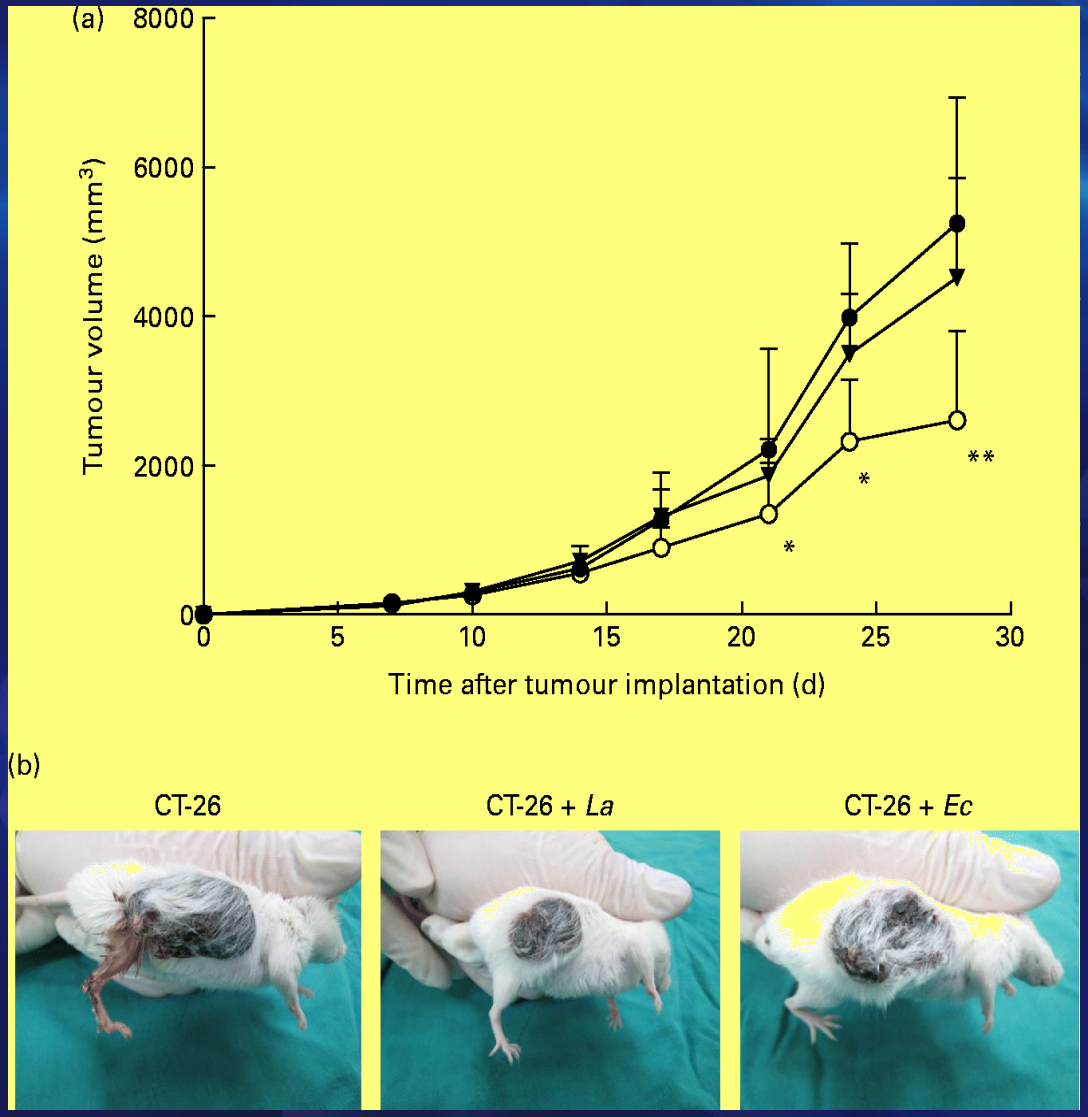
Microwave-inactivated



Baldwin C et. al Nutr Cancer. 2010

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Oral inoculation of probiotics *Lactobacillus acidophilus* NCFM suppresses tumour growth both in segmental orthotopic colon cancer and extra-intestinal tissue



Lactobacillus acidophilus NCFM (*La*) pre-inoculation decreased subcutaneous CT-26 tumour growth.

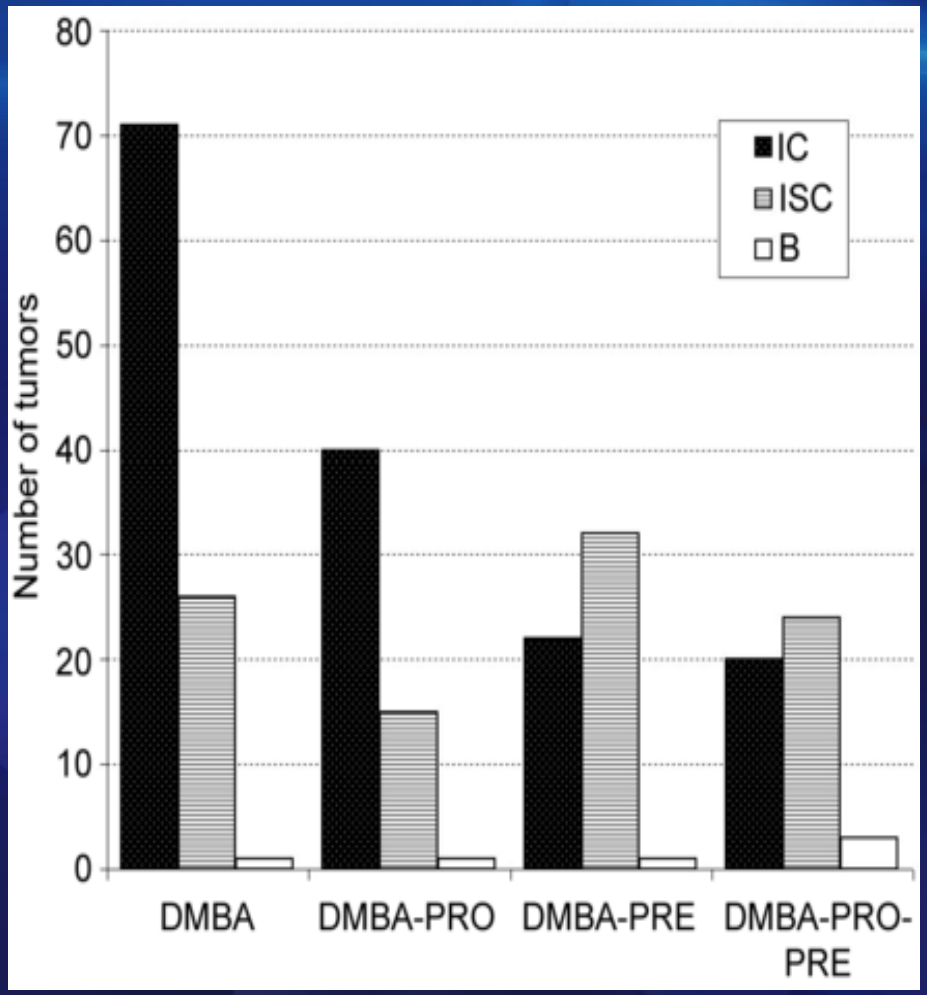
(a) Tumour volumes were determined for CT-26 (), CT-26+*La* () and CT-26+*Ec* () mice.

(b) Representative CT-26, CT-26+*La* and CT-26+*Ec* tumours are shown. CT-26 alone, mice were implanted with CT-26 cells ;CT-26+*La*, mice were pre-inoculated with *La* 1×10^8 colony-forming units (cfu)/mouse per d; CT-26+*Ec*, mice were pre-inoculated with *Escherichia coli* K12 1×10^8 cfu/mouse.

Chien-Chan Chen et. al British Journal of Nutrition 2012

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Preventive effects of probiotic bacteria Lactobacillus plantarum and dietary fiber in rat mammary carcinogenesis.



The PRO-PRE combination :

- lowered tumor incidence (by 17%) lowered tumor volume (by 37%).
- decline tumor frequency per group (by 47%, 47% and 49%, respectively).
- reduce the frequency per animal (by 44%, 41% and 39%, respectively).

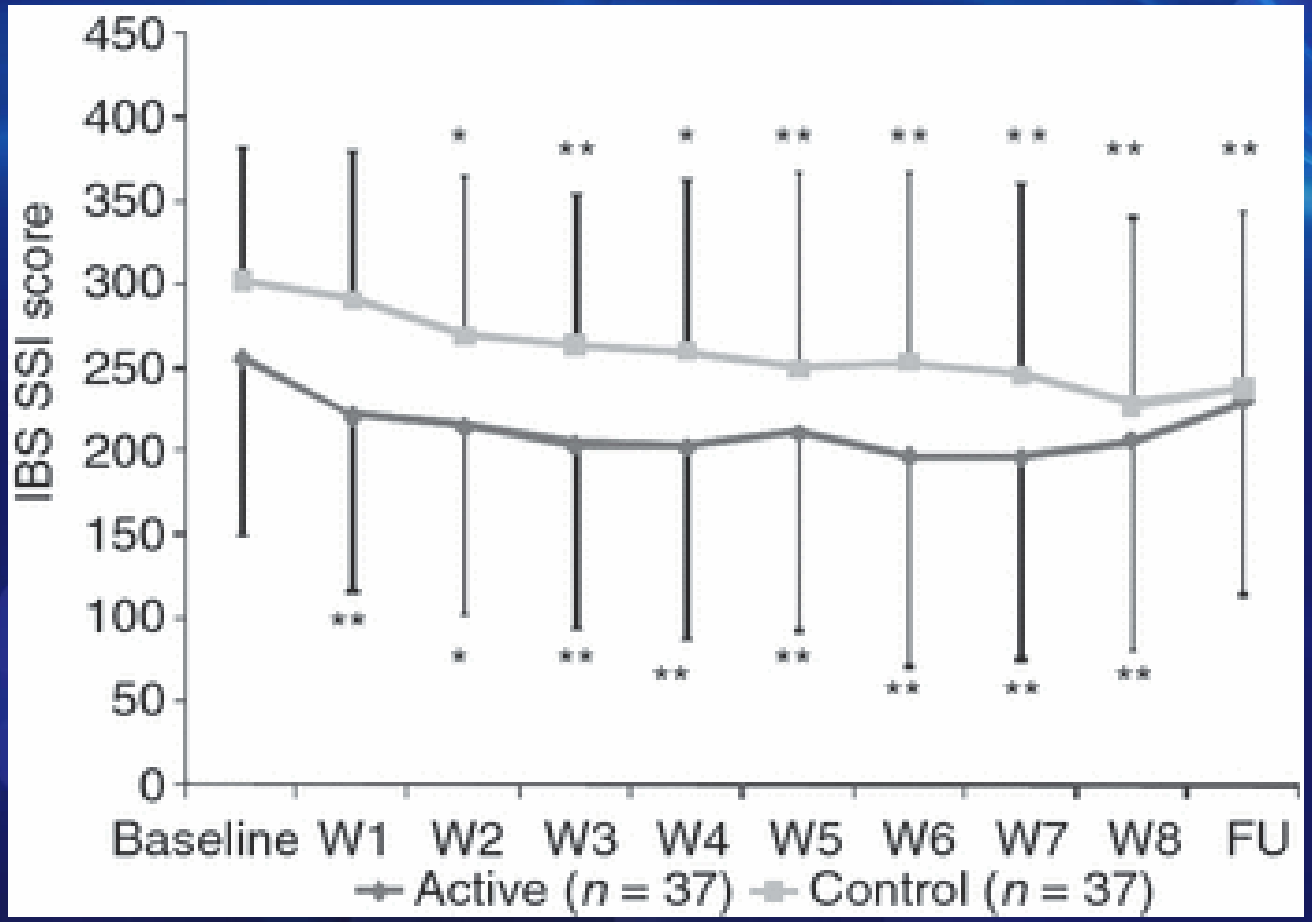
IC: Invasive carcinomas;

ISC: in situ carcinomas;

B: benign lesions

Kassayová M et al Anticancer Res 2014 Sept; 34(9):4969-75.

Clinical trial: the effects of a fermented milk containing three probiotic bacteria in patients with irritable bowel syndrome – a randomized, double-blind, controlled study Sweden



The overall GI symptom severity, assessedby IBS-SSI.

FU=follow-up 8 weeks after the end of the treatment period.

Mean, s.d.
*P < 0.05
**P < 0.01
vs. baseline.

Alimentary Pharmacology & Therapeutics Volume 31, Issue2,, pages 218-227, 26 OCT 2009 DOI: 10.1111/j.1365-2036.2009.04183.x

Abstract

Am J Clin Nutr. 2008 Oct;88(4):1083-7.

Cultured milk, yogurt, and dairy intake in relation to bladder cancer risk in a prospective study of Swedish women and men.

Larsson SC[1], Andersson SO, Johansson JE, Wolk A.

Author information

Abstract

BACKGROUND: Findings from epidemiologic studies of the effect of dairy foods (mainly milk) on the risk of bladder cancer have been inconsistent.

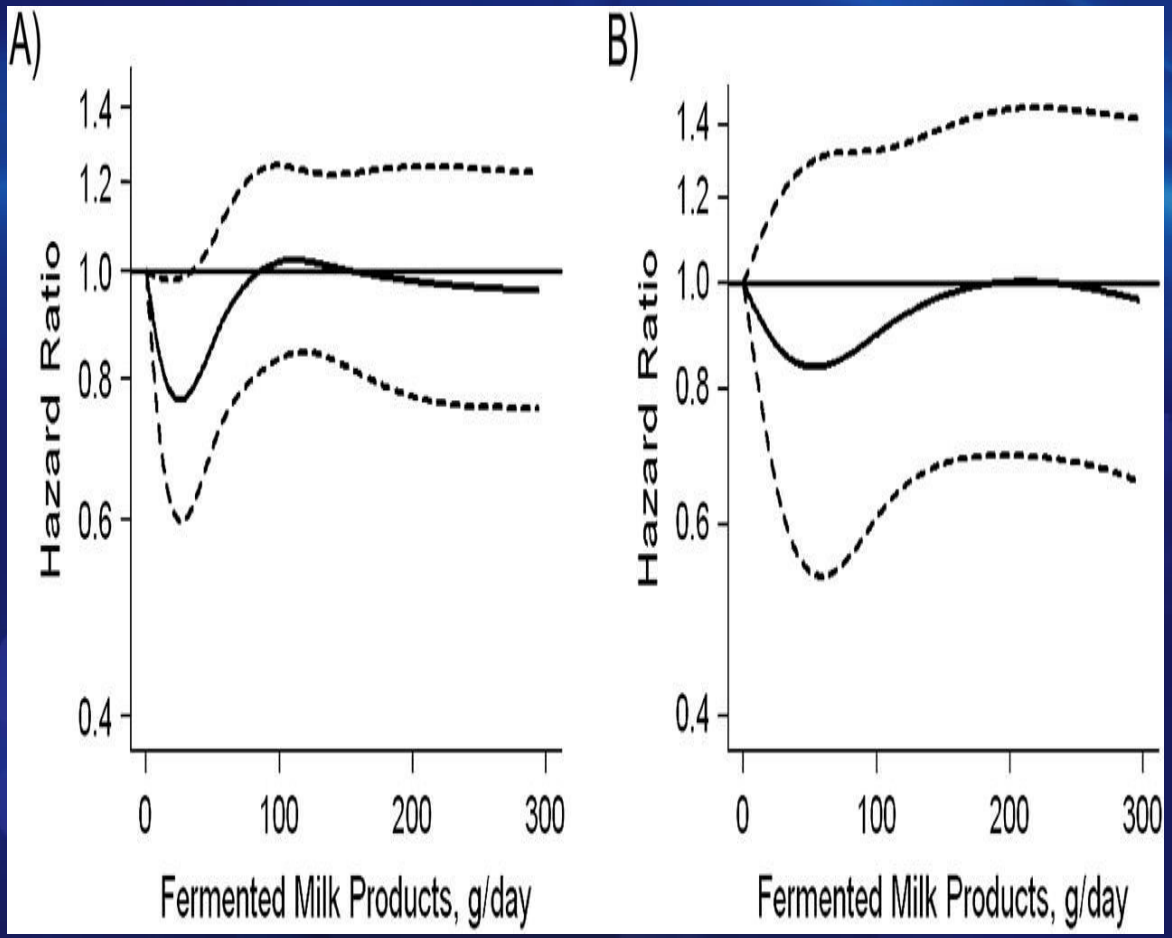
OBJECTIVE: We aimed to examine the association between the intake of cultured milk and other dairy foods and the incidence of bladder cancer in a prospective, population-based cohort.

DESIGN: We prospectively followed 82,002 Swedish women and men who were cancer-free and who completed a 96 i-item food-frequency questionnaire in 1997. Incident cases of bladder cancer were identified in the Swedish cancer registries.

RESULTS: During a mean follow-up of 9.4 y, 485 participants (76 women and 409 men) were diagnosed with bladder cancer. Total dairy intake was not significantly associated with risk of bladder cancer [> or =7.0 servings/d compared with < 3.5 servings/d: multivariate rate ratio (RR) = 0.87; 95% CI: 0.66, 1.15; P for trend = 0.33]. However, a statistically significant inverse association was observed for the intake of cultured milk (sour milk and yogurt). The multivariate RRs for the highest category of cultured milk intake (> or =2 servings/d) compared with the lowest category (0 serving/d) were 0.62 (95% CI: 0.46, 0.85; P for trend = 0.006) in women and men combined, 0.55 (95% CI: 0.25, 1.22; P for trend = 0.06) in women, and 0.64 (95% CI: 0.46, 0.89; P for trend = 0.03) in men. The intake of milk or cheese was not associated with bladder cancer risk.

CONCLUSION: These findings suggest that a high intake of cultured milk may lower the risk of developing bladder cancer.

The Netherlands Cohort Study on Diet and Bladder Cancer, 1986–2002.



Models are adjusted for age, smoking status, number of cigarettes smoked, smoking duration, and intakes of vegetables, fruits, meat, beverages, energy, and fat.

Hazard ratios (solid line) and 95% confidence intervals (dashed lines) for bladder cancer in men (A) and women (B)

András P. Keszei et al. Am. J. Epidemiol. 2009;171:436-446

American Journal of Epidemiology © The Author 2009. Published by Oxford University Press on behalf of the Johns Hopkins Bloomberg School of Public Health. All rights reserved. For permissions, please e-mail: journals.permissions@oxfordjournals.org.

American Journal of EPIDEMIOLOGY

Consumption of Dairy Products and Colorectal Cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC).

Yoghurt

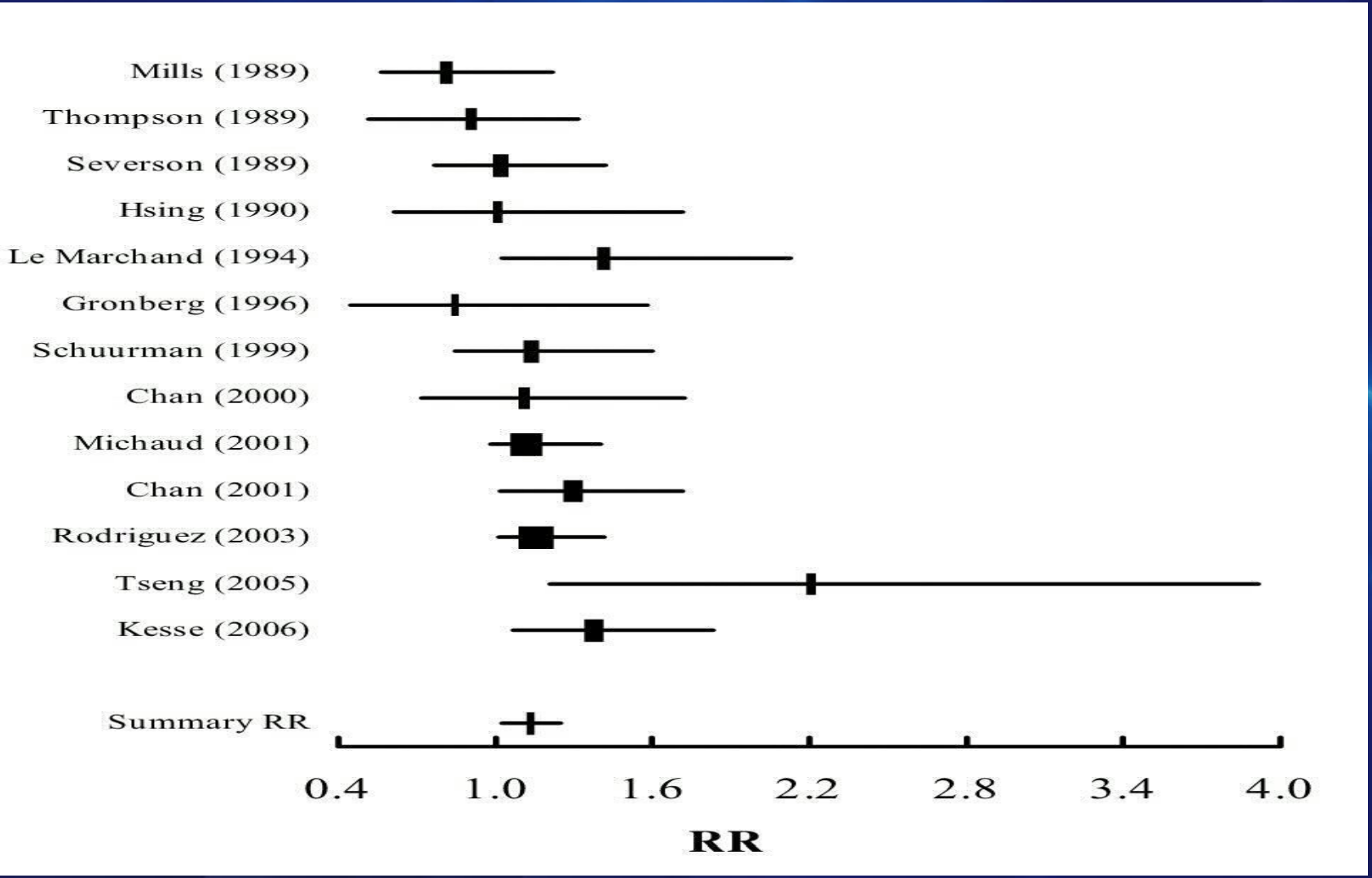
- Yoghurt intake was significantly inversely related to colorectal cancer risk in categorical models (≥109 g/day vs. non-consumers, HR 0.90, 95% CI: 0.81–0.99; *P*-trend =0.043) .The inverse association was restricted to the colon and not observed for tumours in the rectum, although the difference was not statistically significant (*P* Heterogeneity =0.79).

Cheese

- Cheese consumption was inversely associated with colorectal cancer in the categorical model . The association was significant for colon (≥56 g/day vs. <5 g/day HR, 0.83, 95% CI: 0.71–0.97; *P*-trend =0.047) but not rectal cancer, although this difference was not significant (*P* Heterogeneity =0.39).

- Murphy N et. al PLoS One 2013 Sep

Milk Consumption and the Risk of Prostate Cancer



Qin LQ, et al. **Journal** Asia Pac J Clin Nutr. 2007

Milk Consumption and Cancer Risk
World Cancer Research and American Institute for Cancer Research Report 2007

- Probable association between milk intake and lower risk of colorectal cancer

- Probable association between milk intake and increased risk of prostate cancer

- Limited association between milk intake and lower risk of bladder cancer

Conclusions and Future Directions

- Fermented dairy products has shown some benefits in preventing certain types of cancer in cell cultures and animal studies under specific conditions.
- Few cohort and clinical trial shown some benefits for colon and bladder cancer.
- More studies need to establish :
  - the subgroups who would benefit the most and the ones at risk.
  - the most effective synbiotic products,
  - the amount, frequency and duration of consumption to obtain optimal response.
  - other diseases that could be prevented/delayed by the consumption of fermented dairy products.


Thank you for
your attention





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