Evidence for Self-Medication
International Review Journal

Probiotics: quality matters

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Probiotics are a generally safe treatment option and have been evaluated positively for several conditions by the Cochrane Collaboration. However, they must have adequate compositional quality and be able to persist in the gut to be efficacious and safe.

Probiotics are bacteria with beneficial health effects. Their efficacy and safety have been evaluated positively by the Cochrane Collaboration for several indications such as acute infectious diarrhea [1]. However, the Cochrane Collaboration has also noted that individual preparations can differ and "more research is needed to guide the use of particular probiotic regimens". As highlighted in two recent review articles [2, 3], the efficacy and safety of probiotic depends not only on the biological properties of specific bacterial species and their strains, but also on the compositional quality of the preparations and their ability to persist in the gut.

Pharmaceuticals licensed as drugs are subject to rigorous quality controls; this applies not only to small molecules and antibodies, but also to probiotics. However, less stringent regulations are generally applied to preparations categorized as dietary supplement or functional foods. A recent review [2] based on 38 evaluations of 31 marketed probiotic drugs found that in 37% (14/38) of the evaluations the included product contained microorganisms other than those listed in the label, with 18% (7/38) found with contaminants. Moreover, only 29 products declared expected amounts on their label, for which 48% (14/29) were found to have differing amounts of bacteria compared to their respective labels. In total, only 29% (9/31) of the drug products consistently satisfied all three criteria in all studies (**Tab. 1**). The most often tested preparation was a *Bacillus clausii* product (Enterogermina®) that was found to satisfy all three criteria consistently across five separate studies.

A key challenge to orally administered probiotics is that they must survive the passage through the hostile (highly acidic) environment of the stomach to reach the gut in sufficient numbers to become biologically active. This is illustrated by an experimental study in which the survival of several marketed probiotic preparations was tested in three different simulated conditions (two gastric and one intestinal juices) [4]. Among the 10 tested preparations, only three maintained the initial number of microorganisms in two distinct simulated gastric juices and only two in simulated intestinal juice The *B. clausii* product Enterogermina® was the only product which conserved its biological activity in all three tests (**Fig. 1**), which can be attributed to its spore-forming capabilities [4].

A recent systematic review has assessed the survival rate of orally administered probiotic bacteria during gastro-intestinal transit based on clinical studies with 17 studies of single strains and 13 studies of multi-strain products [3]. When the administered dose was higher than 10^{10} colony-forming units/day, the probiotic could be recovered from stool regardless of the strain used. This was independent of treatment duration.

The *B. clausii* product Enterogermina®, despite being studied only after a single administration and at a lower dosage (6 billion CFU [colony forming units] versus probiotics administered up to 100 billion CFU), was among the ones with the highest amount recovered [3]. Such a result appears to confirm in a clinical setting the results observed in the preclinical model [4] and suggests that spores are highly resistant to the harsh conditions of gastro-intestinal transit.

The authors in the end concluded that general dosage recommendations for probiotics by regulatory agencies are not high enough for a strain to survive, persist and be efficacious in the gut. Additionally, it was noted that resistance to gastro-intestinal transit is strain specific, with spore-forming bacteria among the ones with higher survivability and persistence. Of interest, among spore formers included in the study, *B. clausii* appears to have better ability to resist to the gastrointestinal tract [3].

We conclude that greater rigor is required in controlling the pharmaceutical quality of marketed probiotic products and that the same attention should be reserved to fully elucidate the ability of the strain to reach and persists and multiply in the intestine. Such a latter characteristic appears to be strain

Evid Self Med 2022;2:220086 | https://doi.org/10.52778/efsm.22.0086
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Tab. 1. Compliance with the label claims of probiotic drugs marketed worldwide with focus on microbial composition, amount of living cells and presence of contaminant microorganisms. Reproduced with permission from [2].

Product	Manufacturer	Country	Compliance (composition)	Compliance (amount)	Contaminants	Reference
Benegut	Abbott	India	No	No	Yes	Kesavelu et al., 2020
Bifilac	Tablets India Ltd	India	No	Yes	Yes	Kesavelu et al., 2020
Bifilac GG	Tablets India Ltd	India	Yes	Yes	No	Kesavelu et al., 2020
Biogermin	Union Health S.r.l.	Italy	Yes	Yes	No	Celandroni et al., 2019
Codex	Zambon	Italy	Yes	Yes	No	De Vecchi et al., 2008
			Yes	Yes	No	Vecchione et al., 2018
Combiflora	Medopharm	India	No	No	No	Kesavelu et al., 2020
Cyfolac	Karnataka Antib & Pharm Ltd	India	Yes	Yes	No	Kesavelu et al., 2020
Darolac	Aristo Pharmaceuticals Pvt Ltd	India	No	No	No	Kesavelu et al., 2020
Ecogro	Akum Drugs & Pharma	India	No	Yes	Yes	Patrone et al., 2016
Econorm	Dr. Reddy's Laboratories Ltd	India	Yes	N.D.	No	Kesavelu et al., 2020
Entero Plus	Glaxo India Ltd	India	Yes	Yes	No	Kesavelu et al., 2020
Enterogermina	Sanofi	Italy India	Yes	Yes	No	De Vecchi et al., 2008
			Yes	Yes	No	Vecchione et al., 2018
			Yes	Yes	No	Celandroni et al., 2019
			Yes	Yes	No	Patrone et al., 2016
			Yes	Yes	No	Kesavelu et al., 2020
Enterol capsules	Biodiphar	Belgium	Yes	Yes	No	Vanhee et al., 2010
Enterol sachets	Biodiphar	Belgium	Yes	Yes	No	Vanhee et al., 2010
Entromax	Mankind Pharma	India	No	Yes	No	Patrone et al., 2016
GNorm	Nouveau Medicament	India	Yes	N.D.	No	Kesavelu et al., 2020
GutPro	Riata Life Sciences Pvt Ltd	India	Yes	No	No	Kesavelu et al., 2020
Infloran	BERNA	Italy	Yes	No	No	Fasoli et al., 2003
Lacidofil	Merck	Poland	No	Yes	No	Zawistowska-Rojek et al., 2016
			Yes	Yes	No	Korona-Glowniak et al., 2019
Lakcid	Biomed	Poland	Yes	Yes	No	Zawistowska-Rojek et al., 2016
			Yes	Yes	No	Korona-Glowniak et al., 2019
Ospor	Matrix Pharma	Pakistan	Yes	No	No	Patrone et al., 2016
Pre Pro Kid	Fourrts India Laboratories	India	No	No	No	Kesavelu et al., 2020
Pre Pro Kid L	Fourrts India Laboratories	India	No	No	Yes	Kesavelu et al., 2020
Reflora Z	Sundyota Numandis	India	No	No	No	Kesavelu et al., 2020
Regutol	Alembic Pharmaceuticals Ltd	India	No	Yes	Yes	Kesavelu et al., 2020
Remune AI	Sundyota Numandis	India	No	No	No	Kesavelu et al., 2020
SPORLAC	Sanzyme Ltd	India	Yes	No	No	Kesavelu et al., 2020
Super Flora GG	Sundyota Numandis	India	Yes	No	No	Kesavelu et al., 2020
Tufpro	Virchow Biotech Pvt. Ltd.	India	No	No	Yes	Patrone et al., 2016
ViBact	USV	India	No	Yes	Yes	Kesavelu et al., 2020
Vizylac	Torrent Pharmaceuticals Ltd	India	Yes	No	No	Kesavelu et al., 2020

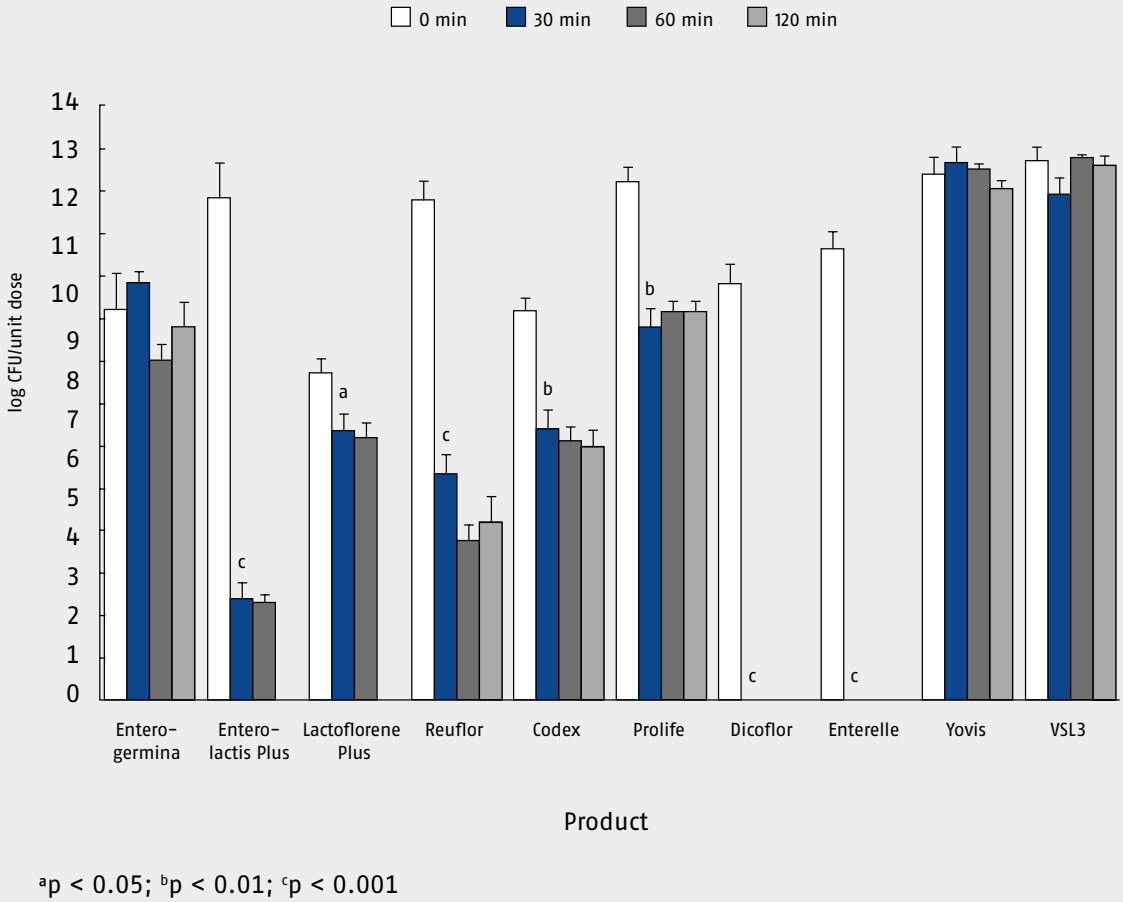

Figure 1. Viability of probiotic formulation after incubation in one of the two simulated gastric fluids. Data are expressed as logarithm of colony-forming units (CFU) of each product. Reproduced with permission from [4].

dependent and poorly affected by the matrix or by the dosage, especially when probiotics are administered in dosages lower that 10 billion CFU. The *B. clausii* product Enterogermina® appears to be one of the few preparations consistently fulfilling the required criteria on compositional quality, survivability and persistence.

Literature

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Conflict of interest: P. Pellegrino and M. III Perez are employees of Sanofi.

Disclosure: Medical writing and publication funded by Sanofi.

Information regarding manuscript

Submitted on: 29.10.2021
Accepted on: 01.04.2022
Published on: 10.04.2022