ARTICLE

How Do We Know When Something Called "Probiotic" Is Really a Probiotic? A Guideline for Consumers and Health Care Professionals

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Probiotics are live microorganisms, which when administered in adequate amounts, confer a health benefit on the host. The evidence for the impact of probiotics on diverse end points of human health is mounting, driving the commercial development of products containing them. Subcategories of the general term *probiotic* include probiotic drug (intended to cure, treat, or prevent disease), probiotic food (which includes foods, food ingredients, and dietary supplements), direct-fed microbial (probiotics for animal use), and designer probiotic (genetically modified probiotics). As there is no legal definition for the term *probiotic*, products labeled "probiotic" on the market may not have been adequately characterized for content, stability, or health effects. This article reviews what a probiotic is (and is not) and what to consider when choosing a probiotic product.

Key words: *probiotic, Lactobacillus, Bifidobacterium, consumers*

What Is a Probiotic?

Probiotics are live microorganisms, which when administered in adequate amounts, confer a health benefit on the host.[1] The key aspects of this definition are shown in Table 1, which include the fact that the microbe must be alive when administered (the fact that they may die during transit through the host does not exclude them) and must have undergone controlled evaluation to document health benefits in the target host (often, but not always, humans). Hamilton-Miller and colleagues provide a historical context for use of this term, including noting that it once referred to microbial-produced substances and the microbes themselves.[2] Table 2 lists the many different definitions for probiotic that have been advanced through the years. Subcategories of the general term *probiotic* include probiotic drugs (intended to cure, treat, or prevent disease), probiotic foods (which include foods, food ingredients, and dietary supplements), direct-fed microbials (probiotics for animal use), and designer probiotics (genetically modified probiotics). Currently, there is no legal definition of the term *probiotic*.

As the field of probiotics has advanced, the types of clinical indications tested for probiotic impact and the range of physiologic status of subjects being tested have greatly expanded. A given probiotic, tested in different clinical situations, might exert a beneficial effect, show no effect, or result in an adverse effect. However, a negative or adverse effect in certain situations does not negate probiotic status. Such results do, however, stress the need to be specific about the benefits that are documented for each probiotic and the situations in which use is considered to pose an undue risk. Use of "probiotic" to describe a strain refers to proven beneficial effects of the strain. Furthermore, it should not be presumed that a probiotic will be effective or safe under all conditions of use.

Are Probiotics Foods or Drugs?

The definition above was issued as part of an expert consultation that specifically dealt with probiotics in food (including water).[8] However, the definition did not include the term "food." Although almost identical to a previously published definition by Guarner and Schaafsma–"live microorganisms, which when consumed in adequate amounts, confer a health effect on the host"[3]—the consultation substituted the word "administered" for "consumed," presumably to expand the concept of probiotics to include administration in ways other than by mouth. Given that food must be consumed orally, the consultation apparently intended that the definition not be

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DOI 10.2310/6180.2009.00002

Table 1. What a Probiotic Is and Is Not

Characteristics of a probiotic	*Comment*
What a probiotic is…	
Microbe	Bacteria and yeast have been studied as probiotics.
Alive	The microbe must be alive when administered, although it may die after administration to the host. Viability at the site of action is presumed to be important, but some effects may be mediated by cell components. Recovery of the fed strain in feces is suggestive that the microbe is alive at active sites within the alimentary canal.
Defined and properly named	The microbe must be identified at the genus, species, and strain levels, according to current nomenclature and using current best methods, generally DNA based. Phenotypic, morphologic, and biochemical characterization contribute to thorough strain characterization.
Safe	A probiotic must be safe for its intended use, as stipulated by regulatory authorities for the category of product. In the case of drugs but not foods, risks are balanced by benefits.
Many possible regulatory categories	"Probiotic" is an overarching category. Subcategories include • Probiotic food (food) • Probiotic supplement (dietary supplement) • Probiotic drug (drug) • Designer probiotic (genetically modified microbe) • Direct-fed microbial (animal uses)
What a probiotic isn't…	
Synonymous with native putatively beneficial microbes	Candidate probiotics are commonly isolated from the pool of native putatively beneficial bacteria found in humans, but it is not correct to equate probiotic and native commensal microbes.
Synonymous with "live active cultures"	Live cultures are microbes associated with foods, often as food fermentation agents. Many of these have not been directly tested for health benefits. Probiotics are live microbes that have been shown to have a health effect. Also, some probiotics would not typically be associated with foods (such as *Escherichia coli*) and as such would not typically be referred to as a "live culture."
Live vaccine Fecal enemas	Although not specifically omitted from the definition, these uses of microbes fall outside the category of probiotics.

DNA = deoxyribonucleic acid.

limited to food or by route of administration (eg, oral, vaginal, topical, rectal). Furthermore, the expert consultation report describes the functions of probiotics, including their role in "alleviation of infectious diseases." This is consistent with much of the literature on probiotics that is focused on what are seen by regulatory bodies as therapeutic end points, such as reduction of duration of infectious diarrhea or extension of remission of pouchitis. In the United States, products that are intended to treat, cure, prevent, or mitigate disease are drugs, not foods. Taken together, it appears that this definition was intended to encompass health maintenance or improvement and therapeutic (ie, both food and drug) uses for probiotics.

An important point must be made from a regulatory perspective. It is tempting to see the character of "food" or "drug" as an inherent property of a substance. However, in the United States, a substance is characterized as a "food" or a "drug" not based on its intrinsic characteristics as much as on its intended use.* A product that by all appearances is a food and may even be available to the general public in grocery stores would be considered a drug by the US Food and Drug Administration (FDA) if it is sold to treat, cure, prevent, or mitigate disease [Food, Drug, and Cosmetic Act of 1938, §201(g)((1)]. Drug status by FDA interpretation is also extended to any product administered along with a drug to either enhance effects or alleviate side effects if the side effects themselves constitute diseases. There are both commercial and scientific ramifications to this regulatory approach. For example, although controlled human studies on "drug" uses for probiotics are numerous, such benefits cannot be claimed for a probiotic marketed as a food or a dietary supplement (a subcategory of foods). This approach imposes limitations on what publicly funded human studies can be conducted on probiotics in the United States. For example, Hickson and colleagues conducted a study in England in which the diet of hospitalized patients undergoing antibiotic treatment over the age of 50 years was supplemented with a commercially

*Some intrinsic properties preclude a substance from being considered a food. For example, oral consumption is a necessary, although not sufficient, characteristic for a food.

Table 2. Various Definitions of Probiotics that Have Been Published and Proposed for Use

Definition	*Reference*
Substances secreted by one microorganism that stimulate another microorganism	63
Tissue extracts that stimulate microbial growth	64
Organisms and substances that have a beneficial effect on the host animal by contributing to its intestinal microbial balance	65
A live microbial feed supplement that beneficially affects the host animal by improving its intestinal microbial balance	66
A viable mono- or mixed culture of microorganisms that, applied to animals or humans, beneficially affects the host by improving the properties of the indigenous microflora	67
A live microbial culture of cultured dairy product that beneficially influences the health and nutrition of the host	68
Viable bacteria, in a single or mixed culture, that have a beneficial effect on the health of the host	69
Living microorganisms that on ingestion in certain numbers exert health benefits beyond inherent basic nutrition	3
A microbial dietary adjuvant that beneficially affects the host physiology by modulating mucosal and systemic immunity, as well as improving nutritional and microbial balance in the intestinal tract	70
A preparation of or a product containing viable, defined microorganisms in sufficient numbers that alter the microflora (by implantation or colonization) in a compartment of the host and by that exert beneficial health effects in this host	71
Live microorganisms, which when administered in adequate amounts, confer a health benefit on the host	1
Specific live or inactivated microbial cultures that have documented targets in reducing the risk of human disease or in their nutritional management	72
Preparation of viable microorganisms that is consumed by humans or other animals with the aim of inducing beneficial effects by qualitatively or quantitatively influencing their gut microflora and/or modifying their immune status	73

available fermented milk.[4] The results showed a significant reduction in antibiotic-associated side effects and *Clostridium difficile*–associated diarrhea. The FDA would view such a study as a drug trial and, if consulted on such a study, would require the filing of an Investigational New Drug application before the study is begun.[5] A predicament arising from this position is that given that foods are not manufactured under drug Good Manufacturing Practices and food companies generally do not have an interest in marketing drugs, Investigational New Drug status may not be pursued. Therefore, a problematic disconnection exists between probiotic uses and the regulatory framework in the United States, even as it pertains to research designed to determine the validity of physician recommendations including, for example, the use of probiotics when taking antibiotics.

What Is Meant by "Health Benefit"?

Key to this definition of probiotic is that it must confer a "health benefit." What might not be as clear is what a "health benefit" encompasses. When broadly interpreted, the term refers to both drug-type effects (eg, mitigation of diarrhea), which may be assessed in healthy or diseased populations, and food-type benefits (such as supporting a healthy immune system), which should be assessed in healthy (including at-risk) populations. Furthermore, from the perspective of the Food and Agriculture Organization of the United Nations (FAO), physiologic effects—generally measured by biomarkers rather than clinical end points—that may correlate with health enhancement also fall under the umbrella of "health effects."[1] For example, alterating gut microbiota and enhancing the production of secretory IgA are included in this category. However, whether demonstration of physiologic effects in the absence of measured consumer benefit is sufficient for substantiating a health benefit claimed for a product depends on specific government regulations. In the United States, the FDA provides nonbinding guidance as to the types of scientific substantiation it recommends with regard to making claims on foods and dietary supplements.[6,7]

Composition of Probiotics

Probiotics in theory can be composed of any live microbe. A large number of probiotics hail from the *Lactobacillus* or *Bifidobacterium* genera. Also popular is *Saccharomyces boulardii* (a yeast). Less commonly used are strains of *Escherichia coli* or *Bacillus coagulans*. One category of microbe that is typically not considered to be a probiotic is a virus. Live viruses have been administered as vaccines, but such use is generally considered to be outside the realm of probiotics.

A distinction should be made between a probiotic and a live, active culture. Fermented foods, especially fermented dairy products, frequently contain live, active cultures. As it is essential that probiotics be documented to have a health benefit, and given that live, active cultures are generally tested only for food fermentation properties and not health benefits, equating live, active cultures and probiotics is not correct. Until the live cultures are shown to confer a health

benefit, they should not be called probiotic. Therefore, not all fermented foods, even those retaining live cultures, should be considered to be probiotic foods. Another misuse of the term *probiotic* comes from equating probiotic with native beneficial bacteria. Given that probiotics must be isolated, characterized, demonstrated to have a health benefit, and then administered, it is not correct to talk about "native probiotic bacteria."

A final consideration with regard to probiotic composition is that probiotics must be defined. The FAO published guidelines for characterizing a probiotic that specifically refer to microbes defined at the strain level.[8] Therefore, this eliminates use of the term *probiotic* to describe undefined combinations of microbes such as fecal enemas, even though a therapeutic benefit has been suggested.[9] The probiotic strain must be properly identified at the genus and species level according to current scientific practices, generally deoxyribonucleic acid (DNA)-based, and properly named according to current nomenclature.[10] Furthermore, strain-specific identification is also necessary. Defined probiotic strains should also be deposited into an international culture collection, which provides the scientific community with the resource to repeat published studies. An international strain deposit also provides a standard for comparison of the probiotic entity over time. The ready availability and affordability of genomic sequencing technology have made a requirement for total genomic sequencing of probiotic strains tenable.[11]

Mechanism and Sites of Probiotic Action

Many definitions of probiotics proposed through the years (see Table 2) are restrictive by stipulating either a mechanism or a site of action (eg, intestinal or extraintestinal). The mechanism of action of probiotics (eg, benefits result from colonizing the intestine or enhancing immune function) has been dropped from the definition, in part, to allow for a product capable of imparting a clear health benefit to be called a probiotic even if the mechanism of action is not fully understood. This is currently the case for many observed effects. Furthermore, this approach does not restrict use of the term to one specific mechanism of action. Requiring that probiotics only impart benefits, for example, by influencing intestinal microbiota, would preclude use of the term for products able to interact directly with immune cells. Some mechanisms of action associated with probiotics are listed in Table 3.

Table 3. Proposed Mechanisms of Action of Probiotics

Produce antimicrobial substances, such as organic acids or bacteriocins
Upregulate immune response (eg, secretory IgA) to possible pathogens or to vaccines
Downregulate inflammatory response
Assist in early programming of the immune system to result in a better balanced immune response and reducing risk of development of allergy
Improve gut mucosal barrier function
Enhance stability or promote recovery of commensal microbiota when perturbed
Modulate host gene expression
Deliver functional proteins (eg, lactase) or enzymes (natural and cloned)
Decrease pathogen adhesion

It is common for probiotic products to be marketed on the premise that they have an important effect on the intestinal microbiota. However, evidence is mixed on the type and extent of impact different probiotics have on the intestinal microbiota.[12–16] One difficulty is that many such studies were conducted using methodologies that relied on the ability to cultivate the microbial components of the colonizing bacterial communities. Given that modern surveys of intestinal microbiota indicate that a majority of resident microbes are not cultivated using conventional culture techniques,[17] studies using culture methods likely have not assayed the impact of probiotics on some dominant members of the intestinal microbial community. A need remains to assess probiotic impact on bacterial communities using culture-independent DNA-based methods. Review of numerous studies on this topic makes a general conclusion on the role of probiotics on gut microbiota difficult at present because studies differ so widely with regard to probiotic strain(s), dose, subject age (from premature infants to elderly), subject health status, and methods used. One generalization that does emerge from these studies is that strains selected for the ability to resist the challenges of stomach acid and pancreaticobiliary secretions in the small intestine are usually recovered alive in feces and often lead to a transient increase in the levels of genus of the fed probiotic.[18] This recovery is typically, although not always,[19] dose dependent.[20] Recovery of the probiotic, with few exceptions, is short-lived once feeding is stopped. Exceptions include Collins and colleagues who noted recovery of *Lactobacillus salivarius* UC118 from one adult test subject 100 days after feeding had stopped, whereas the strain could not be isolated from any of the other 19 subjects 3 weeks postfeeding.[21] Schultz and colleagues documented *Lactobacillus rhamnosus* GG in the feces of two infants 24 months after exposure to the probiotic from their mothers during vaginal delivery.[22] Changes in other microbial groups are generally modest and are reversed once feeding has stopped. There is some evidence that certain probiotic

preparations can temper the impact of antibiotics on intestinal bacterial communities.[23,24] Taken together, probiotics may or may not impact the populations of gut microbiota. However, an influence of a probiotic strain on intestinal microbiota cannot be presumed, and a causal link between such changes and health benefits needs to be established. Furthermore, microbiologic changes can be less important than functional changes.[25] For instance, biochemical parameters, such as lactate, acetate, ammonia, amines, pH, phenols, p-cresol, and enzymatic activities, may be more indicative of health status than alterations in microbial populations.

With regard to site of action, recent studies lead one to appreciate that probiotic function is being assessed in sites outside the intestine.[26] Functional benefits in the oral cavity, stomach, vaginal tract, skin, and systemic immune responses have all been evaluated. Recently, pilot studies have looked at the influence of probiotics on symptoms of vernal keratoconjunctivitis,[27] ultraviolet-exposed skin,[28] and sleep patterns in the elderly.[29]

Not All "Probiotics" Are the Same

Products contain different genera, different species, or even different strains of the same species, and not all products should be expected to work the same. Therefore, claims of efficacy should be target specific and should be made only for products that have been found efficacious in carefully designed studies. The marketplace has many examples of different strains of the same species: *Lactobacillus acidophilus* NCFM and La-1; *L. rhamnosus* GR-1 and GG; *Lactobacillus casei* Shirota and DN-114 001; *Lactobacillus reuteri* RC-14 and ATCC 55730; and *Bifidobacterium lactis* HN019 and BB-12. Each of these strains has a unique dossier to document individual health benefits. It is noteworthy, however, that among dozens of European commercial products, the same biotype (based on pulsed-field gel electrophoresis of chromosomal DNA) was predominant among *Bifidobacterium*-containing products,[30] suggesting that *Bifidobacterium* strains used commercially may not be so diverse.

Head-to-head comparisons of different strains of the same species in clinical settings have not been conducted. However, several studies have compared different commercial probiotic products and documented differences in efficacy. For instance, Weizman and colleagues compared the effects of *B. lactis* BB-12 with those of *L. reuteri* ATCC 55730 on the incidence, duration, and severity of infections among infants in day care.[31] In this randomized, double-blinded, placebo-controlled trial of 201 infants between 4 and 10 months of age, formula was fed containing either no probiotic or BB-12 or ATCC 55730 at levels of 10^7/g dried formula. Infants consuming the BB-12-containing formula showed reduced duration and episodes of fever and reduced episodes and duration of diarrhea. However, only the infants consuming ATCC 55730 also showed fewer clinic visits, reduced absences from the child care center, and lower antibiotic prescriptions.

Another comparative study was conducted on five different commercial probiotic preparations assessing the duration of acute diarrhea in children.[32] Products were composed of *L. rhamnosus* strain GG; *Saccharomyces boulardii*; *Bacillus clausii*; a mixture of *L delbrueckii* var *bulgaricus*, *Streptococcus thermophilus*, *L. acidophilus*, and *Bifidobacterium bifidum*; or *Enterococcus faecium* SF68. The study randomized 571 children (3–36 months of age) who presented with acute diarrhea to receive one of these products or unsupplemented oral rehydration solution for 5 days. The results showed that only the *L. rhamnosus* GG and the product containing a mixture of lactic acid–producing bacterial probiotics were effective at reducing the duration of diarrhea. These studies illustrate that one cannot presume that different commercial probiotic products will perform in the same manner and that an evidence-based approach to product selection is the best approach.

Probiotics Must Be Safe

Probiotics must be safe under the intended conditions of use.[33,34] Factors to consider include the inherent properties of the microbe, the physiologic status of the consumer, the dose administered, and the possibility that the probiotic could be a potential source of genes in the gastrointestinal tract environment that could be transferred to less innocuous members of the colonizing microbiota by horizontal gene transfer. For foods, although 100% safety can never be ensured, probiotics must offer a reasonable certainly for no harm when consumed by the generally healthy population, and an assessment of risk versus benefit is not applicable. By contrast, for drugs, safety also includes balancing possible deleterious side effects with potential benefits. Owing to this clear distinction of safety standards and susceptibility of target populations between foods and drugs, it is advisable to use the term *probiotic drug* when a probiotic is being used on an unhealthy population to cure, treat, or prevent disease.

When considering the safety of commercially available products, probiotic products in the United States are either foods or dietary supplements and as such are targeted for use by the generally healthy population. *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, and *S. thermophilus* all have excellent safety records for such uses. *Lactobacillus* and *Bifidobacterium* species have been recovered from patients with bacteremia,[35] but infection from probiotic

consumption has not been reported in healthy consumers. Some dietary supplement forms of probiotics include species of *Bacillus*, *Clostridium*, *Enterococcus*, and *Escherichia*, genera associated with safety concerns such as toxicity, infectivity, or potential sources of genes that may be transferred to less innocuous members of the commensal microbial community. These genera of bacteria should only be used when the manufacturers adequately demonstrate safety of the specific strain they intend to market for the target populations.

Use of probiotics in either diseased or immunocompromised individuals must be done mindfully. Frequently, controlled studies reporting no product-related adverse incidents have been conducted in unhealthy or at-risk subjects, such as very low birth weight infants,[36] patients with chronic inflammatory bowel diseases,[37,38] intensive care unit patients,[39] and patients with acute infectious diarrhea.[40] Successful outcomes to such studies suggest that the identical product could be used with similar subjects under medical supervision. However, a report of increased mortality in the probiotic-consuming group of a randomized, clinical trial in subjects with acute pancreatitis highlights the importance of care when designing and launching studies with compromised individuals.[41] As a general rule, caution should be used when considering probiotics in newborns, immunocompromised patients, patients with severe underlying illness, or short bowel patients (who are at increased risk of bacterial translocation). Another risk was reported when catheter line contamination leading to fungemia was observed in hospitalized patients given *Saccharomyces*.[42] The manufacturer should be able to provide guidance as to the type and extent of safety assessments that have been conducted on its product.

What to Look For in a Probiotic Product

Choosing probiotic products can be difficult. Several documents have been prepared by professional societies to assist health care professionals and consumers in this process.[43–45] As mentioned previously, probiotic products in the marketplace in the United States are either foods or supplements. These products make different types of relevant claims on their labels and in advertising: content claims and health benefit claims. In the United States, foods and dietary supplements are allowed to make what are called structure or function health benefit claims, which relate the product to a physiologic effect on the normal (not diseased) structure or function of the human body. Such claims are required by statute to be "truthful and not misleading." Therefore, companies making such claims are required to have substantiating scientific documentation. However, the claims are not subjected to premarket regulatory approval. In practice, the FDA does not police the accuracy or degree of substantiation for such claims; therefore, it is likely that some number of commercial products assert unsubstantiated communications on labels, Web sites, or advertising.

With regard to content claims, numerous published articles report independent analysis documenting probiotic products that do not have either the number or the type of microbes claimed on the label.[46] Although Good Manufacturing Practices exist for both foods and dietary supplements,[47,48] products still may not be accurately labeled. Accordingly, it is difficult for the consumer and the health care professional to distinguish the substantiated from the unsubstantiated claim. Guidance on some questions frequently asked by health care professionals and consumers about probiotics can be found at <http://www.usprobiotics.org>. The following provides a framework for considering different commercial products.

Probiotic Claims

Currently, there is no third-party objective rating system for product claims on probiotic products. Most probiotics are sold as either dietary supplements or ingredients in foods and cannot legally declare that they cure, treat, or prevent disease. Therefore, it is common to see claims such as "supports a healthy immune system" or "helps keep your microflora in balance." What comprises a legitimate dossier to substantiate such claims is beyond the scope of this article. However, manufacturers should provide citations to published references that support health benefit claims. The quality of the studies and the extent of the effects observed provide quality of support for the claim. Given that different strains of the same species may have different health effects, it is logical to make certain that claims of health benefits are based on research done on the particular probiotic. The product should contain the specific strain(s) of bacteria at the same levels used in the published supporting research.

Dose

Product effects are also dose specific. It is not possible to provide one "minimum dose" that applies to all probiotics because different probiotics are effective at different levels. Some products are effective at 50 million colony-forming units (CFUs)/day[49] to more than 1 trillion CFU/day.[50] This huge range in effective doses likely reflects differences in strains, clinical end points, and perhaps the best guess of the researcher of what level would be sufficient. Dose-response studies are not common in the probiotic literature database.

Therefore, it is essential that product doses should be based on levels that were tested in human studies and shown to be effective.

Label

The label should disclose the genus, species, and strain designation of each probiotic strain contained in the product. This approach provides a level of confidence that the product manufacturer is formulating the product with specific strains consistently over time. Furthermore, strain designations tie the product content back to the scientific publications that document claimed health effects. The product label should also indicate the number of live microorganisms that are delivered in each serving or dose, as well as an expiration date. Levels are typically communicated as CFUs. The suggested serving size or dose should be indicated. Labels should describe health benefits that have been substantiated for the product. Finally, proper storage conditions and corporate contact information (including a Web site or consumer hotline number where additional information can be obtained) should be indicated.

Medical Recommendations

Efforts to provide clinical recommendations for probiotics were published recently.[51] Meta-analyses of available high-quality studies are also helpful in this regard.[36–40,52–60] However, these efforts are hampered by limited data for many specific probiotic strains. Only 2 of over 25 meta-analyses and systematic reviews published to date focused on specific strains: Szajewska and Mrukowicz's article on *Saccharomyces cerevisiae* var *boulardii* strain Lyo and Szajewska and colleagues' article on *L. rhamnosus* GG.[52,53] The remaining publications have grouped together studies conducted on different probiotic preparations. This approach is not without merit as it indicates which preparations have positive results. However, compelling data suitable for meta-analysis for any one preparation are not available for most probiotics. Sometimes medical recommendations are based on a limited number of positive studies.

Conclusions

The range of probiotic products available to consumers and the science supporting these products are expanding. However, much misinformation also exists about probiotic products, and establishing clinical recommendations can be a complicated process. It is likely that research efforts now under way focused on understanding the role of the human microbiome in health and disease[61] will fuel additional discovery in how probiotics might impact human health.[62] Attention to issues such as the strain specificity of health effects, mechanisms of action, required dose for specific products, safety considerations for certain patients, and understanding product labels can assist both consumers and health care providers in effectively choosing products.

Acknowledgment

Financial disclosure of authors and reviewers: Dr. Sanders is a paid consultant to companies commercially involved in probiotics.

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