

# Sport Supplements and the Athlete's Gut: A Review

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## ABSTRACT

Vigorous or prolonged exercise poses a challenge to gastrointestinal system functioning and is associated with digestive symptoms. This narrative review addresses 1) the potential of dietary supplements to enhance gut function and reduce exercise-associated gastrointestinal symptoms and 2) strategies for reducing gastrointestinal-related side effects resulting from popular sports supplements. Several supplements, including probiotics, glutamine, and bovine colostrum, have been shown to reduce markers of gastrointestinal damage and permeability with exercise. Yet the clinical ramifications of these findings are uncertain, as improvements in symptoms have not been consistently observed. Among these supplements, probiotics modestly reduced exercise-associated gastrointestinal symptoms in a few studies, suggesting they are the most evidenced-based choice for athletes looking to manage such symptoms through supplementation. Carbohydrate, caffeine, and sodium bicarbonate are evidence-based supplements that can trigger gastrointestinal symptoms. Using glucose-fructose mixtures is beneficial when carbohydrate ingestion is high (> 50 g/h) during exercise, and undertaking multiple gut training sessions prior to competition may also be helpful. Approaches for preventing caffeine-induced gastrointestinal disturbances include using low-to-moderate doses (< 500 mg) and avoiding/minimizing exacerbating factors (stress, anxiety, other stimulants, fasting). Adverse gastrointestinal effects of sodium bicarbonate can be avoided by using enteric-coated formulations, low doses (0.2 g/kg), or multi-day loading protocols.

## Introduction

A well-functioning gut is a key, albeit sometimes overlooked, contributor to athlete performance and health. Indeed, increases in gastrointestinal (GI) symptoms correspond with worsened performance [1–3], and certain GI symptoms such as nausea, intestinal cramping, and loose stools can even cause athletes to drop out of competition or be unable to complete an exercise task [4, 5]. Hoffman and Fogard [4], for example, found that Western States 100-mile Endurance Run participants reported nausea and/or vomiting as the leading reason for withdraw from the race. This contrasts with other symptoms (e. g. flatulence, belching) which are unlikely to affect performance or lead to competition withdrawal.

Dietary supplements are frequently used to improve athletic performance, training, and recovery, particularly in elite athletes [6]. Certain supplements (e. g. probiotics, glutamine, bovine colostrum) have been studied as gut function enhancers in the con-

text of exercise [3, 7, 8], and various manufacturers are marketing these and other supplements to exercisers/athletes to improve performance and GI function. Conversely, other sports nutrition supplements have known GI-related side effects that can impair performance or interfere with training in some situations. These include supplements with a long track record of study and use (carbohydrate, caffeine, sodium bicarbonate) as well as more novel products (exogenous ketones). Athletes who decide to use these supplements may need to implement mitigation strategies to minimize GI-related adverse effects and maximize these supplements' ergogenic properties.

Given the widespread use of dietary supplements and their potential impacts on the gut, the aims of this narrative review were twofold: 1) to address the potential of certain dietary supplements to enhance gut function and reduce exercise-associated GI symp-

toms; and 2) to discuss strategies for reducing GI-related side effects from using popular sports nutrition supplements.

## Supplements Purported to Enhance Gut Function with Exercise

### Probiotics

A typical human may host approximately 38 trillion bacteria, with the vast majority residing in the colon [9]. Investigations using both animals and humans have shown the importance of gut microorganisms (particularly bacteria) and the gut microbiome to health [10]. Although gut microbiome research has traditionally focused on its relationships to health and disease, there is growing interest in how it impacts performance and body composition in athletes [11]. Unsurprisingly, administering probiotics (defined as live microorganisms that confer benefits when taken in adequate amounts) has been suggested as a way to manipulate gut microbiome composition and function [12]. Much of the interest in probiotics among athletes is related to their purported ability to reduce GI symptoms during competition, as well as lessen the odds of transitory infectious GI illnesses that interfere with training.

The mechanisms by which probiotics may influence GI function during exercise are varied, including modulation of the immune system via adhesion to the mucosa, stabilization of gut barrier function, improved nutrient absorption, and production of short-chain fatty acids [13]. It is beyond the scope of this review to discuss all these mechanisms in detail, and interested readers are pointed to the following reviews for more detail on proposed mechanisms [13, 14]. Specific to the literature on probiotics and exercise, a major barrier to understanding how probiotics could exert benefits is that most studies have not quantified changes in the gut microbiome itself [13]. Further, the most common method of assessing gut microbiota composition (fecal sampling) may be a poor surrogate for colonization of probiotics in the mucosa [15]. In large part these issues explain why in 2019 the International Society of Sports Nutrition (ISSN) reported in a position stand that the mechanisms of probiotics remain largely unknown in the setting of sport and exercise [13].

Recent reviews have summarized the effectiveness of probiotics for GI-related outcomes in athletes and regular exercisers [13, 16, 17], with a summary of conclusions in ► **Table 1**. In general, these reviews reported some positive results (e. g. reduced GI symptoms, altered markers of GI permeability), but findings have been marked by inconsistency and substantial differences in methodology. One investigation that illustrates this inconsistency is West et al. [18], who found that taking *Lactobacillus fermentum* for 11 weeks increased the number and duration of mild GI-symptom episodes, yet reduced the severity of such episodes. Differences in study methodology have come in the form of the probiotic species and strains used, dosages and durations of supplementation, and approaches to measuring and defining GI symptoms and illnesses [13].

It is notable that among the studies to show reductions in GI symptoms with probiotic use in athletes, the benefits have been modest [3, 19]. These observed modest benefits in athletes parallel the magnitude of symptom improvements observed in non-ath-

► **Table 1** Overview of recent position statements and reviews on probiotic use in sports and exercise.

Source	Summary of Conclusions
IOC Consensus Statement on Dietary Supplements [16]	Additional evidence is required to document the effectiveness for reducing GI distress and infections
International Society of Sports Nutrition Position Stand on Probiotics [13]	A small number of trials have evaluated GI outcomes in athletes/exercisers, with largely mixed results due to variation in methodology
Möller et al. systematic review [17]	Three of the identified studies showed somewhat positive effects on GI symptoms, but the results were mixed and not consistent

GI, gastrointestinal; IOC, International Olympic Committee.

letes; a meta-analysis by Ford et al. [20], for instance, reported a standardized mean difference of  $-0.31$  in global symptom scores when comparing combination probiotics against placebo in irritable bowel syndrome patients. Consequently, athletes who use probiotics should have realistic expectations about the likely size of benefit to be obtained. In addition, research on probiotics and direct measures of physical performance (strength, endurance, speed, etc.) is limited, with largely unconvincing data, particularly in trained athletes [13].

If an athlete uses a probiotic despite the mixed evidence, they should keep several considerations in mind. First, with respect to safety, there is general agreement that probiotics are safe in healthy individuals, and that individuals with certain conditions (HIV, severe acute pancreatitis, liver diseases) are perhaps at higher risk of moderate-to-serious adverse events [13]. Second, probiotics from the *Bifidobacterium* and *Lactobacillus* genera are best studied [13, 21], meaning that efficacy and safety data for specific species and strains is most likely to be available for products that contain these bacteria. Third, others have suggested that probiotics' benefits are dependent on achieving a minimum duration (2–4 weeks) of supplementation [13, 22]. In terms of dosage, the ISSN's position stand on probiotics notes that doses usually fall between  $1 \times 10^9$  and  $1 \times 10^{11}$  colony forming units (CFUs) per day [13]. Likewise, the IOC's consensus statement on dietary supplements reported moderate evidence for probiotics when taken for several weeks at  $10^{11}$  CFUs/day [16]. Looking across these groups' recommendations, it can be concluded that supplementing for two or more weeks with a probiotic containing *Bifidobacterium*- and *Lactobacillus*-based species at  $10^9$  and  $10^{11}$  CFUs/day may be required to obtain benefits.

Importantly, there are likely to be interactions between dose, duration of supplementation, and the probiotic species and strain(s) used [13]. Moreover, these interactions may depend on the specific outcome being measured. Indeed, a review of probiotic meta-analyses reported that higher dosages (e. g.  $> 10^{10}$  CFUs) were more beneficial than lower dosages for preventing antibiotic-associated diarrhea and lowering blood pressure, but dose-response effects were absent for other outcomes (e. g. *Clostridium difficile*-associated diarrhea, atopic dermatitis) [23]. Additionally, *Lactobacillus rhamnosus* GG reportedly exhibited dose-response effects in acute pediatric gastroenteritis, but two other strains did

not [23]. Unfortunately, dose-response studies in athletes are largely non-existent [13], so making conclusions about these interactions as they relate to probiotic use in sports is not yet possible.

## Glutamine

Glutamine is the most abundant amino acid in plasma and is found in skeletal muscle [24]. It is a key substrate for rapidly proliferating cells, including GI cells [25]. Over half of ingested glutamine is sequestered by the splanchnic bed and never enters systemic blood [26], and most of this sequestered glutamine is used for oxidative purposes [27]. It has been proposed that situations leading to high glutamine utilization (trauma, illness, extreme/heavy exercise) and its subsequent depletion contribute negatively to changes in GI barrier integrity [28]. In turn, GI barrier dysfunction is hypothesized to induce endotoxemia and systemic inflammatory responses, which have been tied to a higher rate of exercise-associated GI symptoms in some, but not all, studies [29]. In addition, reduced gut barrier integrity could provoke GI symptoms by leading to the malabsorption of ingested nutrients [29]. In theory, then, ingesting glutamine before or during exercise could maintain gut function and reduce GI symptoms through several mechanisms, including maintaining mucosal thickness, limiting the release of pro-inflammatory cytokines, and activating protein kinases that regulate the expression of tight junction proteins [25].

Zuhl et al. [7] supplemented eight endurance-trained adults with 0.9 g/kg of fat-free mass of glutamine for seven days prior to 60 minutes of running at 65–70%  $\dot{V}O_2$ max in 30 °C, 12–20% relative humidity conditions. Participants also completed the protocol with a glutamine-free placebo, and condition order was randomized. Overall, glutamine reduced exercise-induced intestinal permeability (as measured through a sugar-probe test) versus placebo. Similarly, another study showed that glutamine supplementation (0.9 g/kg of fat-free mass) two hours before 60 minutes of running in the heat reduces intestinal permeability versus placebo [30]. Pugh et al. [31] essentially repeated this acute experiment, except they used varying doses (0.25, 0.5 and 0.9 g/kg of fat-free mass); overall, they confirmed that a high dose reduces GI permeability versus placebo, with lower doses also possibly having small-to-moderate benefits.

Collectively, these experiments point to glutamine as effective for reducing GI permeability. However, the placebos used in these three studies were sugar-free drinks and devoid of carbohydrate or protein, which is important given that administration of these macronutrients reduces GI permeability with exercise as compared to water [32]. In addition, Lambert et al. [33] found that a 6% carbohydrate beverage with a small amount of glutamine (0.6%) did not reduce gut permeability markers as compared to the carbohydrate beverage alone when subjects ran for 60 minutes at 70%  $\dot{V}O_2$ max in temperate conditions. This was also true when aspirin was ingested, which is known to increase GI permeability. Other evidence indicates that reliance of intestinal cells on glutamine may be diminished when both glutamine and glucose are available [34]. Consequently, it remains unclear whether glutamine offers any additional benefits to GI barrier function when carbohydrate (or protein) is ingested during prolonged exercise.

Another caveat to consider is that these studies either failed to assess GI symptoms [7, 30] or did not find differences in GI symptoms between conditions [31]. Of note, a recent tolerance study found that glutamine, particularly at high doses (0.6–0.9 g/kg of fat-free mass), induces mild-moderate GI symptoms in a substantial proportion of people (e. g. > 50%) over the initial two hours post-supplementation [35]. Given the lack of data showing an improvement in GI symptoms with glutamine, its clinical utility among athletes remains speculative. Future work should use validated questionnaires (e. g. [36]) to assess the occurrence of exercise-associated GI symptoms with glutamine versus placebo. Ideally, placebos should provide a source of energy, such as glucose, maltodextrin, or whole protein. Finally, studies conducted in naturalistic sporting environments are warranted, as the literature is largely limited to laboratory settings.

## Bovine Colostrum

Colostrum is the fluid produced by mammary glands following parturition and is markedly different from mature milk, in that it is lower in lactose and higher in protein, growth factors, enzymes, enzyme inhibitors, cytokines, and nucleotides [37]. The components of bovine colostrum have been proposed to favorably alter gut integrity and resilience through several mechanisms, including reducing apoptosis signaling and bolstering tight junctions via actions on transmembrane proteins such as occludin and claudin [38]. Experiments conducted in the late 1990s and early 2000s showed that administering bovine colostrum to rodents reduced GI injury from non-steroidal anti-inflammatory drugs and heat exposure [39, 40], providing a strong impetus for human research. Given the increases in GI permeability that occur with intense and prolonged exercise (especially in the heat) [32], bovine colostrum has received considerable interest as gut-barrier-enhancer over the past decade.

The evidence supporting bovine colostrum for mitigating exercise-induced gut-barrier dysfunction has been somewhat positive but mixed, with several studies showing gut barrier biomarker improvements [41–45], others reporting null findings [8, 46], and one reporting an increase in GI permeability [47]. Notably, the doses used have been extremely variable, with lower and upper amounts of 0.5 g/day [45] and ~130 g/day [8], respectively. The most common dose is 20 g/day [42–44, 46], typically taken for two weeks. No clear dose-response relationship is apparent across the literature, as the lowest daily dose was associated with improvements in gut barrier biomarkers [45] while the highest daily dose did not elicit benefits [8]. One potential explanation for the lack of dose-response relationship across studies is that the concentration/activity of bioactive compounds in bovine colostrum varies markedly [48].

As is the case with glutamine research, the cited bovine colostrum experiments largely neglected to assess GI symptoms [41–44, 46]. Among those that did evaluate subjective GI complaints, symptom occurrence with bovine colostrum was not significantly different than placebo [8, 45, 47]. In contrast to the glutamine studies that used sugar-free, non/low-caloric placebos, the selection of placebos has been better in these bovine colostrum experiments (milk protein concentrate [41–44]; skim milk and milk protein [46];

dehydrated whey and banana [45]; concentrated whey protein [47]; corn flour [8]).

The totality of evidence indicates that supplementing up to 20 g/day with bovine colostrum for at least 1–2 weeks may reduce GI permeability from prolonged and/or intense exercise in some situations, but its clinical utility is uncertain given the lack of benefits on subjective GI symptoms. Other controlled studies have found some improvements in physical performance and immune function (reduced respiratory infection risk or severity) with bovine colostrum, particularly during intensified training periods [48]. Thus, supplementation may be worthwhile for some athletes, but athletes who undergo doping control tests should know that the World Anti-Doping Agency (WADA) recommends against using bovine colostrum because it is a source of insulin-like growth factor (IGF)-1 [48]. However, the soundness of WADA's recommendation has been questioned, and interested readers may refer to Davison [48] for additional information on the controversy.

### Other Potential GI Barrier Enhancers

Several additional nutrients and nutraceuticals have been investigated for their effects on exercise-induced changes in GI barrier integrity. Supplementation with vitamin C (1 g) two hours before exercise was found to reduce exercise-induced increases in plasma lipopolysaccharide [49], a marker of endotoxemia that correlates with GI barrier permeability [50]. Likewise, 14 days of zinc carnosine supplementation (37.5 mg, twice daily) reduced post-exercise intestinal permeability by 71 % in comparison to placebo, possibly through the enhancement of tight junction formation and stability [44]. Ingesting 10 g of L-citrulline, which is a non-proteinogenic amino acid that acts as a precursor to arginine, 30 minutes prior to exercise was shown in one randomized, crossover trial to reduce splanchnic hypoperfusion and a marker of enterocyte damage (intestinal fatty acid binding protein) in comparison to L-alanine, though intestinal permeability via a sugar probe test was unaffected [51]. Three days of supplementing with 500 mg/day of curcumin, the principle bioactive component of turmeric, was also shown in a crossover experiment to reduce the rise in intestinal fatty acid binding protein with 60 minutes of running in the heat [52]. As is the case with glutamine and bovine colostrum, the practical relevance of using these supplements to prevent or reduce subjective GI complaints is unknown, primarily due to failure of these investigations to assess GI symptoms in a systematic manner.

Other nutritional substances have been investigated in relation to GI permeability in non-athletes or animal models but are yet to be tested as it relates to exercise-induced gut barrier dysfunction in humans, including vitamin D, vitamin A, and short-chain fatty acids [53]. These may be targets for future study, but for now there is little that can be concluded regarding their relevance to the management of exercise-related GI dysfunction.

### Ginger

The plant *Zingiber officinale* is the source of ginger, a spice used over millennia for its purported health effects [54]. As it relates to athletes and exercise, ginger has been most studied as an analgesic and recovery supplement, with several randomized trials demonstrating benefits on muscle soreness and pain [55, 56]. In contrast, little attention has been paid to the possible GI benefits of ginger

in the context of exercise, despite there being abundant literature on its gut-influencing properties in clinical and non-athlete populations [57].

Ginger is a 5-HT<sub>3</sub> antagonist [58], which partly explains why it may reduce nausea in several contexts (pregnancy, chemotherapy, motion sickness) [59]. Anecdotally, ginger is used as an anti-emetic by ultra-endurance athletes [60], but to date, its use in that setting has not been evaluated in a published randomized trial. An abstract from a 2015 scientific meeting reported that consuming a ginger-containing sports drink before 5-km running slightly reduced nausea post-run relative to a placebo and water [61]. Given the causes of exercise-related nausea can vary considerably [62], it will be important for future studies to examine the potential anti-emetic effects of ginger in a range of exercise settings (e. g. sprinting, interval exercise, ultra-exercise, in the heat, etc.).

Although ginger may reduce nausea in certain situations, other trials have found the rate of GI-related side effects to be higher with ginger than placebo. Altman and Marcussen [63] found that daily ginger supplementation led to more mild-moderate GI adverse events (e. g. eructation, dyspepsia). In addition, a meta-analysis of randomized trials on the use of ginger for symptomatic osteoarthritis relief revealed that the withdrawal rate due to adverse events was higher than with placebo, with most events being related to bad taste or types of GI upset [64]. Notably, dosages ranged from 0.5–1.0 g/day [64]; hence, even small doses can lead to side effects in susceptible individuals. Athletes who plan to utilize ginger to mollify exercise-related nausea will need to weigh the (unverified) benefits against the potential for GI side effects like burping, heartburn, dyspepsia, etc. Consequently, these athletes should trial low doses (e. g. 0.5 g) before and during training sessions, increasing the dose gradually to determine the likelihood and severity of side effects.

In the author's judgment, athletes suffering from frequent bouts of nausea and vomiting should be evaluated for potential underlying causative conditions or diseases. Assuming no underlying, identifiable, treatable conditions are identified, these athletes may consider ginger as a relatively low risk treatment despite the lack of evidence around its efficacy. This recommendation is based on the fact that 1) side effects of ginger are almost always transitory/mild [65] and 2) there are currently few other evidence-based treatments for exercise-induced nausea and vomiting [62].

### Summary

► **Figure 1** provides a concise overview of the evidence base behind the dietary supplements discussed, specific to their effects on GI barrier biomarkers and symptoms. Although multiple supplements have been shown to reduce biomarkers of GI barrier damage/dysfunction, the volume and consistency of evidence varies. To date, glutamine and bovine colostrum have the most supportive evidence, in that more than half of investigations found positive effects. (The author acknowledges this approach to evaluating strength of evidence is limited, but it nonetheless provides some indication of where the literature stands.) As depicted in ► **Fig. 1**, the evidence is either very limited or nonexistent as it relates to these supplements' impacts on subjective GI symptoms. Probiotics have some limited support, but due to the multitude of species/strains, formulations, and doses that can be utilized, straightforward

	Probiotics	Glutamine	Bovine Colostrum	Vitamin C	Zinc Carnosine	L-citrulline	Curcumin	Ginger
↓ GI Permeability / Enhances GI Integrity with Exercise	✓	✓✓	✓✓	✓	✓	✓	✓	?
↓ Exercise-Associated GI Symptoms	✓	X	X	?	?	?	?	?

► **Fig. 1** Summary of evidence for nutritional supplements that may have some positive effects on gut barrier integrity and/or GI symptoms. A single check mark indicates very limited favorable or mixed evidence, while two check marks indicate that the majority of studies (more than half) have found positive effects. A question mark indicates that the effects are largely unknown, primarily due to a lack of evaluation. An X represents a general lack of benefit among available studies.

ward recommendations remain elusive. Lastly, ► **Table 2** displays an overview of the supplements' proposed mechanisms as well as practical considerations, including typical dosing used in the relevant literature and potential side effects.

## Supplements that Cause Gut Symptoms

### Carbohydrate

Despite their well-documented use as ergogenic aids, exogenous carbohydrate supplements can exacerbate GI symptoms, which, in severe cases, can lead to worsened performance or dropping out of competition. In general, the GI-symptom-inducing effects of carbohydrate are dependent on dose. For example, Triplett et al. [66] found that seven of nine participants reported their stomachs did not feel as if they were emptying and were very full when they ingested an exceptionally high amount of glucose (144 g/h) during prolonged cycling. Another experiment showed that high carbohydrate gel intake (1.4 g/min) during 16-km runs induced more severe nausea than an intake of 1.0 g/min [67]. Likewise, increasing carbohydrate concentration of a beverage often leads to more severe GI symptoms like bloating, fullness, and side ache [68, 69]. In terms of delivery form, bars may induce more GI symptoms than carbohydrate gels and beverages during intense exercise [2].

One strategy to reduce GI symptoms associated exogenous carbohydrate ingestion is using mixed glucose-fructose products/foods [70]. Glucose and fructose rely on separate, saturable transporters for intestinal absorption, and when carbohydrate intakes exceed 50–60 g/h, supplying carbohydrate as a glucose-fructose mixture (as opposed to a single saccharide) enhances stomach emptying and reduces malabsorption and its associated symptoms [70]. In practice, it can be a challenge to determine the glucose-to-fructose ratio of any given product or food since there is no labeling requirement in the United States to list amounts of individual saccharides, but Wilson et al. [71] does provide estimates of the glucose-to-fructose ratio of 80 different foods and products used during a 70.3-mile triathlon.

Another way to manage carbohydrate-associated GI problems is training the gut. Repeatedly exposing the gut to high carbohydrate intakes may lead to several positive physiological adaptations,

including enhanced gastric emptying, upregulation of intestinal transporters, and greater exogenous carbohydrate oxidation [72]. To date, limited experimental evidence has documented that gut training with carbohydrate supplements reduces GI symptoms and malabsorption when athletes ingest high rates of carbohydrate (e. g. [73, 74]). Performance improvements occurred in one trial [73], but this may be an overstated effect given the improvement was relative to a baseline test in which participants experienced considerable GI symptoms due to the high carbohydrate intake. Further, there is uncertainty as to how gut training should be optimally implemented since prior investigations devoted large proportions of training volume over 1–2 weeks to gut training sessions, which may not be realistic for many high-level athletes. Still, for athletes planning to ingest a high rate of carbohydrate, it is prudent to implement some form of gut training in the weeks preceding competition.

The ingestion of carbohydrate-hydrogel (sodium alginate and/or pectin) products has recently received much attention to manage GI symptoms associated with carbohydrate feeding. The basic principle is that when a carbohydrate-alginate/pectin mixture enters the stomach, the low pH environment causes a gel to form and encapsulate the carbohydrate, which may lessen activation of saccharide receptors in the proximal duodenum [75]. This, in turn, may facilitate stomach emptying and absorption of fluid and carbohydrate. Yet, of the available randomized trials on carbohydrate-hydrogel ingestion during exercise, most have not found physiological, GI, or performance benefits relative to standard carbohydrate formulations [76]. The main exception is Rowe et al. [77], who found that, in comparison to a non-hydrogel carbohydrate (glucose-fructose) beverage, ingesting a carbohydrate-hydrogel beverage at 90 g/h during two hours of running at 68 %  $\dot{V}O_2$ max led to less GI distress, greater exogenous carbohydrate oxidation, and improved subsequent 5-km time trial performance. Clearly, more research is needed to better understand which situations carbohydrate-hydrogel products may offer benefits in terms of GI function and performance.

### Caffeine

Meta-analyses report that caffeine improves physical performance across a variety of exercise types (e. g. [78]). Even so, caffeine's potential side effects – which include GI-related effects – should be considered when designing a supplementation regimen. At high doses ( $\geq 500$  mg), caffeine may induce nausea in some individuals [79], and this can interfere with the completion of exercise in extreme cases [80]. Other factors may amplify the risk of caffeine-induced nausea, including mixing it with other stimulants or taking it when fasted or anxious [62]. Notably, although caffeine has improved performance in numerous studies, most of these investigations were not carried out under conditions of high mental stress and anxiety that often accompany real-life competition [81]. In order to minimize the risk of caffeine-induced nausea, athletes should take an individualized approach to supplementation that considers their individual tolerance and the situation (low- vs. high-stakes competition).

Beyond nausea, caffeine can also exacerbate other GI symptoms such as intestinal cramping, urges to defecate, etc. Withdrawing high caffeine intakes, for example, has been observed to lead to

► **Table 2** Description of mechanisms, dosing/formulation considerations, and possible side effects of supplements that may have favorable gastrointestinal effects.

	Probiotics	Glutamine	Bovine Colostrum	Vitamin C	Zinc Carnosine	L-citrulline	Curcumin	Ginger
<b>Gut mechanism(s)</b>	Immune system modulation, gut barrier stabilization, improved nutrient absorption, short-chain fatty acid production	Mucosal thickness maintenance, pro-inflammatory cytokine modulation, tight junction protein expression	Apoptosis signaling, tight junction protein regulation	Reduced oxidative stress, decreased endotoxemia	Apoptosis signaling, tight junction protein regulation	Splanchnic blood flow maintenance via increased arginine for nitric oxide-induced vasodilatation	Cytokine modulation, apoptosis signaling, reduced oxidative stress	5-HT <sub>3</sub> receptor antagonism
<b>Typical formulations</b>	Capsules, milk-based drinks, powder sachets	Powders mixed with fluid, capsules	Powders mixed with fluid, capsules	Capsules, tablets	Capsules, tablets, powder sachets	Powders mixed with fluid, capsules	Capsules, tablets	Capsules, chewable tablets, powders
<b>Dosing</b>	10 <sup>9</sup> –10 <sup>11</sup> CFUs/day for >2 weeks, usually from <i>Bifidobacteria</i> and <i>Lactobacillus</i> species	0.25–0.9 g/kg of body mass daily or 1 h before exercise	Up to 20 g/day for ≥ 1–2 weeks	1 g, 2 h before exercise	37.5 mg x 2 daily, for 2 weeks	10 g, 30 min prior to exercise	0.5 g/day for 3 days	0.5–2 g daily or prior to acute nausea-provoking stimuli
<b>Possible side effects</b>	Mild GI symptoms, systemic infections, immune system stimulation	Mild-moderate GI symptoms at high doses	GI complaints, skin rashes	Diarrhea, nausea, GI complaints at high doses (≥ 2 g)	GI upset	Stomach discomfort	GI complaints, yellow stools	Belching, stomach upset, heartburn

less GI complaints [82]. In one crossover study, a daily caffeine dose of 3 mg/kg of body mass resulted in higher ratings of “GI distress” relative to placebo over much of a 20-day period [83]. In a sport-specific wrestling study, a high dose of caffeine (10 mg/kg) given before simulated competition led to higher GI complaints and discomfort than a moderate dose or placebo [84]. Unfortunately, these studies did not distinguish between different GI symptoms, and a general lack of controlled research on caffeine’s GI-related side effects means there is uncertainty as to which symptoms are most likely to occur, especially during exercise. Although caffeine (particularly from coffee) has a reputation for increasing intestinal motility, promoting defecation, and causing loose stools [85], the evidence for this in humans is rather limited [86].

Due to a lack of data on the GI-side-effect profile of caffeine in the context of exercise, recommendations for avoiding GI disturbances from caffeine use currently lack specificity. As pointed out by others, there is much inter-individuality in the physiological and performance responses to caffeine ingestion, partly due to genetic differences [81]. It is reasonable to speculate that, as is the case with caffeine’s performance effects, its GI effects may be dictated by (yet to be identified) genes. Until more data are available, current recommendations include: 1) avoiding high doses (> 5 mg/kg of body mass); 2) managing exacerbating factors (psychological stress, anxiety, other stimulants, etc.); and 3) trialing different dosages and timings of ingestion to develop an individual side-effect profile.

As it relates to reducing caffeine’s GI side effects, one interesting area of future research is the use of caffeinated gum as a delivery method. Studies generally show that caffeine delivered via gum appears in the bloodstream more quickly than swallowed caffeine [87]. This could be advantageous because direct contact of caffeine with intestinal tissue may mediate some of its effects on the GI tract [88], meaning that bypassing the intestinal tract could reduce GI side effects. To date, however, this hypothesis remains unverified.

### Sodium Bicarbonate

The evidence underpinning sodium bicarbonate ingestion for high-intensity exercise performance and muscular endurance is strong, with meta-analyses reporting favorable standardized effects sizes of approximately 0.4 [89, 90]. Yet, few athletes report using it [91, 92]. In a survey of elite and sub-elite Dutch athletes, only 4.2% had ever used it, with less than 1% reporting use in the previous four weeks [91]. Likewise, in a survey of elite Japanese track and field athletes, none reported using sodium bicarbonate [92].

One potentially important explanation for this infrequent use of sodium bicarbonate is its tendency to cause GI disturbances. In 1992, McNaughton [93] reported that a 0.3-g/kg of body mass dose exerted the most favorable effects on maximal 60-second cycling performance, while higher doses caused GI disturbances without further improving performance. Subsequent research has shown that, with typical sodium bicarbonate solutions, upper GI symptoms (e. g. nausea, bloating) usually peak 30–60 min post-ingestion, while lower GI symptoms (e. g. bowel urgency, diarrhea) tend to peak 60–90 min post-ingestion [94]. The exact nature and timing of the GI-symptom peak, however, varies depending on sev-

eral factors, including dose, delivery form (capsules vs. solution), and whether food is co-ingested [95].

Neutralization of bicarbonate by stomach acid seems to play a key role in the generation of upper GI symptoms through the production of CO<sub>2</sub>, which results in bloating, nausea, reflux, etc. [96]. Thus, enteric-coated formulations have been purported to reduce GI symptoms since neutralization of bicarbonate in the stomach is largely bypassed. Indeed, a pair of crossover trials by Hilton et al. [97, 98] showed that enteric-coated and delayed-release formulations reduced the typical GI symptoms associated with sodium bicarbonate while still eliciting increases in blood bicarbonate anion concentrations. In addition, an enteric-coated formulation led to an equivalent improvement in 4-km cycling performance with a lower incidence of GI symptoms as compared to sodium bicarbonate in gelatin capsules [99].

There are several other strategies that lessen sodium bicarbonate's GI side-effect profile. An athlete can use a multi-day loading regimen [100], which typically involves ingesting smaller doses (0.1 g/kg of body mass) 3–5 times daily for 5–7 days, with a few hours between doses [101]. Although less research has examined this type of strategy, most results to date have been favorable [102]. Another approach is to simply use a smaller acute pre-exercise dose (0.2 g/kg of body mass) than what is often stated as the optimal dose (0.3 g/kg of body mass) [103]. While a 0.3-g/kg dose may lead to better average performance for a group of athletes, a 0.2-g/kg dose may be superior for athletes who have moderate-to-severe GI symptoms with sodium bicarbonate [104]. Lastly, ingesting sodium bicarbonate with carbohydrate-rich foods may reduce its associated GI symptoms [95].

## Exogenous Ketones

Ketones are lipid-derived compounds produced by the liver in situations of very low dietary carbohydrate intake or starvation [105]. There is growing interest in using exogenous ketones to improve performance, particularly in endurance sports, and there have been reports of teams utilizing them at the Tour de France recently [106]. Although some experimental evidence suggests that ingesting ketones can alter substrate use and perhaps spare muscle glycogen, effects on performance have been inconsistent, with some studies showing positive effects [107] but others showing neutral or even harmful effects [108–110]. While the reasons for the equivocal results are probably multifactorial in nature, one explanation is that GI problems from supplementation may override any metabolic benefits in some situations [109]. This type of scenario was demonstrated by Leckey et al. [110], who showed that, as compared to placebo, pre-exercise ketone diester ingestion (2 × 250 mg/kg) led to GI symptoms in all participants (ranging from mild to severe) and a 2% impairment in 31-km cycling performance. Other investigations have also reported greater GI symptoms during exercise with exogenous ketone ingestion than placebo [111].

Still, others have argued that different choices can be made around ketone form, dose, timing, and frequency of ingestion to minimize GI-related side effects during exercise [112]. Stubbs et al. [113] reported that ketone consumption (in the form of ketone salts or monoester) at rest led to mild (on average) transient GI symptoms, and during prolonged cycling, a ketone monoester

beverage did not lead to greater GI symptoms as compared to an iso-caloric carbohydrate beverage. In general, ketone salts elicit worse GI symptoms than other forms, as do high doses of all types of ketones [109, 112]. Yet, as can be seen in the graphs of individual responses in Stubbs et al. [113], there is substantial inter-individuality in GI symptoms even at a high dose of ketone salts (some people had no symptoms). As such, athletes should trial a variety of supplement protocols during training before implementing exogenous ketone use in competition.

## Concluding Remarks

A well-functioning GI tract is needed for digestion, absorption, and assimilation of ingested energy and nutrients before and during exercise. Intense and/or prolonged exercise causes physiological disturbances to the gut that contribute to symptoms, which, in some cases, interfere with performance. Several supplements, including probiotics, glutamine, and bovine colostrum, have been studied as GI-function enhancers with exercise. Despite some evidence that they may help maintain GI barrier integrity, the clinical ramifications of these findings are uncertain, as improvements in GI symptoms have not been consistently observed. Among these supplements, probiotics modestly reduced GI symptoms in exercisers and athletes in a few studies, suggesting they may be the leading choice for athletes looking to manage GI symptoms through supplementation. Future studies on glutamine should use energy-matched carbohydrate placebos to examine whether glutamine provides unique benefits to gut barrier function. Additionally, future work on glutamine and other supposed gut-barrier enhancers (bovine colostrum, zinc carnosine, vitamin C, L-citrulline, curcumin) must incorporate valid assessments of GI symptomology into their designs in order to evaluate the true practical meaningfulness of these supplements to athletes.

Although they are ergogenic, carbohydrate, caffeine, and sodium bicarbonate can also trigger GI symptoms. Ingesting glucose-fructose mixtures is advantageous when the carbohydrate ingestion rate is high, and undertaking gut training sessions over the weeks preceding competition may also be helpful, though research on such protocols is sparse. The main strategies for preventing caffeine-induced GI issues include avoiding high doses (> 5 mg/kg) and minimizing exacerbating factors (stress, anxiety, other stimulants, fasting). Sodium bicarbonate's GI side effects can be lessened by using low acute doses (0.2 g/kg), enteric-coated formulations, and multi-day loading protocols.

## Conflict of Interest

The authors declare that they have no conflict of interest.

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