ABSTRACT: Uric acid is an essential compound in the body which in normal physiological ranges has potent anti-oxidant capacity while in excess leads to hyperuricemia, a clinical indicator of pro-oxidant and pro-inflammatory state. Uric acid is acquired through purine catabolism and dietary factors (alcohol or fructose-rich drinks) and its physiological balance is maintained by its secretion through the liver and kidney. Any imbalance in either process leads to either the accumulation (hyperuricemia) or reduction (hypouricemia) in uric acid serum levels. Both conditions are associated with disease states, though whether uric acid levels are causative or result of disease remains unclear. Hyperuricemia has become more common in the modern population and causes uric acid to precipitate around joints resulting in gout. A number of pharmacological treatments are currently available for gout, but have many adverse side effects. Due to this shortcoming, new areas of research are exploring better therapies for hyperuricemia including the manipulation of the gut microbiome with probiotics and prebiotics. There is ample clinical and epidemiological evidence supporting the role of prebiotics and probiotics in reducing uric acid levels in serum, though the mechanisms remain elusive. Probiotics can influence the bioavailability of the uric acid’s precursor, namely purine and it breakdown products inosine and guanosine, which could influence clinical uric acid profiles. Overall, there is a need for more sustainable treatment plans for hyperuricemia as uric acid dependent gout continues to rise and the use of the dietary factors probiotics and prebiotics is a strong candidate.

KEY WORDS: Gout, Hyperuricemia, Prebiotics, Probiotics, Purines, Synbiotics

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INTRODUCTION

Uric acid (2,6,8 trioxypurine) is an organic molecule that is either consumed or synthesized in the liver and adipose tissue from endogenously produced purines by the action of the enzyme, xanthine-oxidoreductase (Maiuolo et al., 2016). Uric acid is excreted by the kidneys (65-75%) and intestines (25-35%) and it is this synthesis-excretion balance that determines the balance of uric acid in the body (Maiuolo et al., 2016). In most mammals, uric acid is primarily degraded by uricase to allantoin maintaining low uric acid serum levels (0.5-2.0 mg/dL). However, during the Miocene epoch (8-20 million years ago) of human evolution, humans and our hominid ancestors experienced complete loss of uricase gene through a series of mutations (Alvarez-Lario and Macarron-Vicente, 2010) resulting in uric acid being the end product of purine metabolism.

It has been thought that the evolutionary advantages for the loss of uricase was the protection from oxidation and compensation for mutations in the L-gulono-γ-lactone oxidase (GLO) gene, which resulted in the loss of our ability to synthesize anti-oxidant vitamin C during the Paleocene period (56-66 MYA) (Alvarez-Lario and Macarron-Vicente, 2010, Drouin et al., 2011). Due to its double bonds, uric acid has excellent anti-oxidant capacity, and it is thought to be responsible for two-thirds of our total plasma antioxidant capacity (Ames et al., 1981). Many experimental human studies support the beneficial effects of endogenous as well
as exogenous uric acid (Bhattacharyya et al., 2016; Vieru et al., 2016; Llull et al., 2016; Waring et al., 2001; Waring et al., 2003. Waring et al., 2006). Bhattacharyya and co-workers observed a persistent elevation of plasma antioxidant capacity, uric acid levels and improvement in clinical outcome in Parkinson’s patients receiving oral inosine, a uric acid precursor (Bhattacharyya et al., 2016). In another study, a similar correlation was made between serum uric acid content and disease progression in Parkinson’s patients receiving L-DOPA treatment (Vieru et al., 2016). A further support for the role of oxidative stress in the pathophysiology of inflammatory and neurodegenerative diseases and antioxidant role of uric acid comes from a preliminary observation by Llull et al. (2016). This study reports encouraging neuroprotective effects of uric acid therapy in acute ischemic stroke patients. Beyond the central nervous system, uric acid has been shown to reduce exercise-induced oxidative stress in healthy adults (Waring et al., 2003), increase serum antioxidant capacity in healthy volunteers (Waring et al., 2001), and restore endothelial function in patients with type 1 diabetes or who were regular smokers (Waring et al., 2006).

While the loss of the uricase gene may have helped early humans by providing an elevated anti-oxidant ability, it did not prove so for the modern humans who have experienced major changes in diet and lifestyle particularly during the last several decades. In the human plasma, the normal range of uric acid varies widely and is reported to be 2.5-8.0 mg/dL, 1.9-7.5 mg/dL, and 3.0-4.0 mg/dL for men, women and prepubertal children, respectively (Williamson et al., 2011). This wide variation is a reflection of multiplicity of factors (age, gender, puberty, menopausal status) affecting uric acid synthesis and excretion. Generally speaking, uric acid concentrations in plasma above and below the normal range are considered abnormal and generally referred to as hyperuricemia and hypouricemia, respectively (de Oliveira and Burini, 2012). While most humans have “normal” uric acid levels in the 4 to 7 mg/dL range, some individuals have serum uric acid levels exceeding 7 mg/dL. A prolonged uric acid access at these levels tend to increase the risk for a deposit of crystalline uric acid at the surface of joints or in skin or cartilage leading to gouty attacks. The reasons for “gout-level” hyperuricemia are complex and poorly understood. Historically, the rise in prevalence of hyperuricemia and gout has paralleled with rise in obesity, consumption of purine-rich diet (meat, seafood), fructose and alcohol (de Oliveira and Burini, 2012; de Oliveira et al., 2013). In addition, the rise in obesity has affected the efficiency of uric acid excretion and thus an epidemic of rising blood uric acid levels (Yamashita et al., 1986; Matsuura et al., 1998). These epidemiologic observations suggest that both elevated synthesis and diminished excretion of uric acid may be responsible for rise in hyperuricemia. Most importantly, what is not understood is why some individuals overproduce uric acid. It is well known that hereditary hyperactivity of the purine synthesis enzyme PRPP (5-phospho-D-ribose-1-pyrophosphate) synthase can lead to hyperuricemia (Becker et al., 1988), as can partial deficiency of HGPR (hypoxanthine-guanine phosphoribosyl) transferase (Torres and Puig, 2007), the rate-limiting step in the purine salvage pathway.

Currently, a number of pharmacological agents are available to control uric acid levels. Even with their benefits, this form of treatment has shown to have many side effects. For this reason, research needs to investigate alternative treatments in order to avoid adverse side effects. One area of interest that is showing potential is the use of prebiotics and probiotics.

**TWO FACES OF URIC ACID: ANTI-OXIDANT OR PRO-OXIDANT?**

There are enough data in the literature to make a strong case for uric acid as an anti-oxidant as well as a pro-oxidant. Therefore, both low and high blood uric acid levels have been suggested to have health consequences. For example, gout has a complex relationship with hyperuricemia, as hyperuricemia does not always result in gout, however gout always co-exists with hyperuricemia. Clinically, uric acid is regarded as a pro-oxidant or proinflammatory indicator. This bias largely comes from epidemiologic observation implicating hyperuricemia in a number of non-communicable diseases and conditions generally associated with enhanced oxidative state including hypertension, cardiovascular disease, myocardial infarction, stroke, and renal disease (Jossa et al., 1994; Freedman et al., 1995; Kang et al., 2002; Choi et al., 2005; Boss et al., 2006). Results of such observational studies suggest an association, but not a cause-effect relationship between uric acid content and pro-oxidant related disease. Studies have failed to identify whether uric acid elevation is consequent rather than causative of these conditions or acts as an independent risk factor of disease development (Bagheri et al., 2016). It remains unclear whether elevation in uric acid concentration contributes to disease development or is simply a biomarker. Alternatively, uric acid levels could compensate for the pro-oxidant state with the aforementioned conditions. An increase in serum uric acid concentration could be an indication of other risk factors of cardiovascular disease, hypertension, and renal disease that themselves may be associated with elevated serum uric acid levels (Lee et al., 1995; Puig et al., 1991). However, there are many other reports associating uric acid concentration to be an independent risk factor of development of non-communicable metabolic diseases, even after adjusting for these other factors (Jossa et al., 1994; Bos et al., 2006). There remains a strong possibility that uric acid could play a pathogenic role in hypertension, cardiovascular disease and renal disease. In addition, recent studies have found that an elevated serum uric acid concentration as a child is associated with increased blood pressure as an adult and is likely to contribute to the development of early onset essential hypertension (Alper et al., 2005).

On the contrary, several protective effects of exogenous uric acid have been indicated on central nervous system-related diseases (Bhattacharyya et al., 2016; Vieru et al., 2016; Llull et al., 2016), while reduction in the levels of endogenous...
uric acid has been associated with diseases such as multiple sclerosis (Spitsin et al., 2001a; Spitsin et al., 2001b; Tonev et al., 2002; Rentzos et al., 2006), optic neuritis (Knapp et al., 2004), Parkinson’s disease (Church and Ward, 1994; de Lau et al., 2005), and Alzheimer’s disease (Kim et al., 2006).

Like observed associations between non-communicable metabolic and neurodegenerative and/or neurologic disease, it is uncertain whether low serum uric acid level is a cause or a consequence of these diseases. It is conceivable that those with low serum uric acid levels are unable to protect against free radical toxicity, leading to the development of inflammation and the destruction of neuronal tissues. However, it is also conceivable that the hyper-inflammation associated with multiple sclerosis leads to the consumption of uric acid to scavenge the excess free radicals produced, resulting in a lower uric acid level (Drulovic et al., 2001).

Due to the negative impact hyperuricemia can have on an individual’s health, it is important to investigate different treatment methods. It is also imperative that the chosen method of treatment does not have many adverse effects which can just harm one’s health in another way.

**PHARMACOLOGIC MANAGEMENT OF HYPERURICEMIA: CONCERNS**

The overall prevalence of a symptomatic hyperuricemia is 20–25% in adult men, depending on the population studied, with smaller proportions among women (Zhu et al., 2011). A prolonged rise in serum uric acid ≥ 7 mg/dL may lead to the precipitation of urate crystals in and around peripheral joints resulting into gout or gouty conditions (Terkeltaub et al., 2010). In 2008, the prevalence of gout was estimated at 3.9% from the NHANES survey (Chandratte et al., 2013). From the Global Burden of Disease 2012 study, the global prevalence of gout was estimated at 0.08% (Smith et al., 2014).

The burden of gout and hyperuricemia is rising globally and probably more rapidly in USA. This perhaps results from aging world populations and the global change in diet and lifestyle. This also enforces a serious need for search of a better and safe management of hyperuricemia.

Although there is no known causal relationship between hyperuricemia and higher incidence of metabolic disorders such as diabetes, metabolic syndrome and others, a prolonged state of hyperuricemia at ≥ 7 mg/dL definitely increases risk for developing gout (Jossa et al., 1994; Freedman et al., 1995; Harris et al., 1999; Kang et al., 2002; Choi et al., 2005; Boss et al., 2006). Currently, treatment of hyperuricemia is not recommended if the subject is asymptomatic; however, the presence of prolonged hyperuricemia needs to be monitored. A balance between its synthesis and excretion controls the state of uricemia and, therefore, pharmacologic management also makes use of drugs that affect both synthesis (allopurinol, febuxostat) and degradation (rasburicase, Uricozyme®) and excretion (probencid, oseltamivir). Although drugs currently in use for the management of hyperuricemia are safe and efficacious, all possess a number of side effects that are different for patients and therefore, need a particular vigilance (McDonagh et al., 2014; Shu et al., 2016). The side-effects of uric acid lowering therapy is of particular concern in subjects with reduced anti-oxidant load due to G6PD deficiency and these subjects develop serious cases of methemoglobinemia and hemolytic anemia (Ducros et al., 1991; Patte et al., 2002; Bosly et al., 2003; Bhat et al., 2008; Borininstein et al., 2008; Joly et al., 2009; Bain, 2010; Ng et al., 2011; Sonbol et al., 2012; Vadhan-Raj et al., 2012; Zaramella et al., 2013; Cheah et al., 2013). It was estimated in 2008 that greater than 400 million people (over 6% of the world population) were affected by G6PD deficiency, which confers a degree of protection against severe malaria (Cappellini and Fiorelli, 2008; Ruwende and Hill, 1998). This further underscores a need for the search for alternative therapy for management of hyperuricemia.

All current pharmacologic agents used to lower serum uric acid are based on inhibition of its synthesis (xanthine oxidase inhibitors e.g., allopurinol and Febuxostat), augmentation of excretion (uricosuric agents e.g., probenecid, Lesinurad), or its catabolism (recombinant uricase e.g., Rasburicase and Pegloticase) (Anonymous, 2013). All of these agents need to be administered to hyperuricemic subjects on a long-term basis and therefore, raise the risk of adverse side effects. These side effects vary widely based the agent used and the patient. Briefly, it includes, abdominal pain, diarrhea, nausea, skin rash to severe hypersensitivity and others (Anonymous, 2013).

Most subjects with low-grade hyperuricemia remain asymptomatic and never develop gout, stones or have an increased risk for metabolic disease. Therefore, considering risk-benefit ratio treatment of asymptomatic hyperuricemia is not warranted. However, the subjects with significant elevation in uric acid (5–7 mg/dL), but within normal range, may need to be followed and treated if the level of hyperuricemia persists. Since treatment of hyperuricemia is a long-term commitment, there is a need for exploring nutritional and lifestyle modification approaches, as well as other forms of therapy to avoid use of pharmacologic agents.

**DIETARY MANAGEMENT OF HYPERURICEMIA**

**PREBIOTICS AND HYPERURICEMIA**

In recent years, it has been shown that a change in lifestyle has a significant influence on the development of hyperuricemia and may help achieve a healthy whole body uric acid load (Macdonald et al., 1978; Woods et al., 1972; Zima et al., 1993). Based on data from several large epidemiological studies, recommendations for reducing hyperuricemia and gout risk through lifestyle modification have been suggested (Table 1). Most of the data that led to the recommendation have come from observation or small clinical trials and therefore, the mechanism of hyperuricemia reduction (decreased synthesis, increase excretion, or increased uric acid breakdown) remains to be thoroughly explored. There is an extensive amount of data in the literature on the reduction of hyperuricemia by inhibiting its uric acid synthesis using uncharacterized plant
Hyperuricemia, Gout and Probiotics

and food extracts both in vitro and animal studies (Kong et al., 2000; Yan et al., 2008; Chen et al., 2011; Motamarri et al., 2012; Nile and Park, 2013; Kumar et al., 2014; Cock, 2015; Usharani et al., 2016). Unfortunately, almost all of these studies lack any counterpart human study as well as toxicity and safety information.

Both prebiotics and dietary fibers have multiple common health benefits. This has led to an erroneous understanding that prebiotics and dietary fibers are synonymous. Most prebiotics are fibers, but not all fibers are prebiotics. Health benefits of high fiber diets have been known since ancient times. In 430 BC, Hippocrates described the laxative effects of coarse wheat in comparison with refined wheat (Lloyd, 1978). The term “dietary fiber” was first coined by Hippsley in 1953 to describe carbohydrate polymers with 10 or more monomeric units, which are not hydrolyzed by the endogenous enzymes in the human intestine (Hippsley et al., 1953). Today the important role of dietary fibers in human nutrition for disease prevention is undisputed (Slavin et al., 2013).

The concept of prebiotics was defined as non-digestible food ingredients that improve host health by selectively stimulating the growth and/or activity of a select group of bacteria in the colon that provide beneficial metabolites for better health (Gibson and Roberfroid, 1995; Gibson et al., 2004). All prebiotics have some common characteristics including, i) resistance to gastric acidity, hydrolysis by mammalian enzymes, and absorption in the upper gastrointestinal tract; ii) amenable to fermentation by intestinal microflora to produce short-chain fatty acids; and iii) ability to stimulate the growth and/or activity of intestinal bacteria potentially associated with health and well-being (Slavin, 2013). There is a long list of non-digestible and fermentable fibers that qualify as prebiotics. These include, wheat dextrin, inulin, galactooligosaccharides (a synthetic prebiotic), acacia gum, psyllium, and others as well as foods that naturally contain these fibers [see Table 2 of Slavin, 2013].

Inclusion of prebiotic ingredients in the diet has been reported...
to have a variety of health benefits such as the enhancement of immune function (Schley and Field, 2002), reduction in the prevalence and duration of infectious and antibiotic-associated diarrhea (Szajewska et al., 2012), reduction in the inflammation and symptoms associated with inflammatory bowel disease (Guarner, 2007), prevention of colon cancer (Reddy, 1999), enhancement of the bioavailability and uptake of minerals including calcium, magnesium, and possibly iron (Scholz-Ahrens et al., 2001), reduction in risk factors for cardiovascular disease (Slavin 2013), and promotion of satiety, weight loss and possibly prevention of obesity (Carnahan et al., 2014). Although the mechanisms underlying diverse health benefits of probiotics are yet to be fully understood, it may include one or more of the followings: improvement in gut barrier function and host immunity, reduction of potentially pathogenic bacteria subpopulations (e.g., Clostridia spp.), elevation of healthy symbiotic gut microbiota (e.g. Lactobacillus spp. or Bifidobacterium spp.) and increase in short-chain fatty acid production (Cummings et al., 2001; Venuto et al., 2010).

As discussed earlier in this review, a number of observational and in vitro studies have independently associated both uric acid and dietary fibers (prebiotics) with the outcome of inflammatory metabolic disorders (Jossa et al., 1994; Freedman et al., 1995; Kang et al., 2002; Schley and Field, 2002; Choi et al., 2005; Boss et al., 2006; Slavin 2013; Carnahan et al., 2014). Therefore, as a logical extension, many have investigated role of probiotic ingredients and foods rich in these ingredients in uricemia. Results summarized in Table 2 show that prebiotics lower uric acid levels through mechanisms that are largely unknown. It is important to note however, that results of all studies reported here come from observational studies in humans (Chrysohoou et al., 2011; Zykova et al., 2015) or experimental studies conducted in animals only (Koguchi et al., 2004; Auclair et al., 2008; Lin et al., 2014).

**PROBIOTICS AND HYPERURICEMIA**

The pioneering work of Prakash and Chang beginning in the early 1970s opened a future for the use of microencapsulated designer probiotic bacteria as well as enzymes for reducing human metabolic wastes associated with uremia in renal insufficiency. These wastes include ammonia, creatinine, uric acid, phosphate, potassium, magnesium, sodium, chloride, and cholesterol as well as symptoms including liver failure, phenylketonuria, and Crohn’s disease (Chang and Loa, 1970; Chang, 1995; Jain et al., 2009). Today, the use of probiotics as a possible therapy for hyperuricemia is a keen area of research. Probiotic bacteria of the *Lactobacillus* and *Bifidobacterium* genera reduce inflammation and hyperuricemia in murine models (Bai et al., 2014; Ming et al., 2014; Vieira et al., 2015; Chen et al., 2016; Yang et al., 2016). The mechanism by which probiotics reduce hyperuricemia is still being studied, and not completely understood. However, it is currently suggested that probiotics can control uptake of certain compounds which are needed for the synthesis of uric acid. Uric acid production in the body is done through the breakdown of purine nucleotides. If, however, the purine nucleotides were less available, the synthesis of uric acid would reduce as well. This is where probiotic administration comes into play. During the metabolism of purine, two intermediates form, inosine and guanosine. A recent study found that certain probiotic strains, specifically from the lactobacillus genus, are able to degrade inosine and guanosine. With the reduction of these intermediate products, uric acid synthesis would also reduce. This reduction would lead to less uric acid being present, and hence can serve as a possible therapy for hyperuricemia. (Ming et al., 2014). Probiotics can also be modified in order for them to obtain a certain ability they did not initially poses. A study done by Bai et al. modified *Lactobacillus delbrueckii* ssp. *bulgaricus* through uremic serum induction followed by mutations using physical and chemical methods. After doing so, the mutated bacteria were observed to degrade uric acid as well as other uremic toxins (Bai et al., 2014).

One issue that does arise from oral consumption of probiotics is the harsh conditions of the gastrointestinal tract, specifically that of the stomach. One way to overcome this obstacle would be to encapsulate the probiotic prior to its consumption. This form of protection would increase the viability of the probiotics, and hence ameliorate their efficacy, as suggested by a study done by Prakash et al. This study used alginate-poly-L-lysine-alginate (APA) capsules to encapsulate *Escherichia coli* DH5 cells and then administered them to rats. It should be noted that the *E. coli* DH5 cells were genetically engineered to contain the urease gene. It was observed that uric acid plasma concentrations were significantly reduced in the rats that received a daily dosage of APA-encapsulated bacteria when compared to the control. This reduction continued as long as the daily treatment was provided (Prakash et al., 2000).

It should be further noted that other diseases have been associated with elevated blood uric acid concentrations. One such disease is the non-alcoholic fatty liver Disease. A study done by Bhathena et al. investigated the use of APA encapsulated probiotics as a possible therapy for this illness. This study observed that encapsulated *L. fermentum* ATCC 11976 was able to reduce serum uric acid concentrations throughout probiotic administration (Bhathena et al., 2013). Hyperurecemia is also found in renal failure as mentioned before. Coussa et al. investigated the therapeutic efficacy of *Saccharomyces cerevisiae* cells in respect to renal failure. Similar to previous studies, APA capsules were used to encapsulate these cells and were then orally administer them to rats. At the end of this study, it was observed that urea concentrations were reduced over the duration of the treatment. Once the treatment was suspended, urea concentrations began to increase again further indicating that the *Saccharomyces cerevisiae* cells were responsible for urea reduction. However, it should be noted that this study found this form of treatment to have no significant change in uric acid concentrations (Coussa et al., 2010).

The above studies focused on the prevention and treatment of hyperurecemia. In certain situations, the damages of hyperurecemia are already present, such as gout formation,
which is caused by uric acid precipitation around joints. In such scenarios, it would be beneficial if probiotics can serve as a form of therapy. A study by Vieira et al. found that daily administration of *Bifidobacterium longum* 51A was able to alleviate inflammatory parameters, which are associated with gout (Vieira et al., 2015).

From the above studies it can be seen that there is a potential for probiotics to be used as a therapy for hyperuricemia and the illnesses it causes. Even with the information obtained from the above studies, most of our knowledge and experience with use of probiotics in managing hyperuricemia in humans largely comes from patients with renal insufficiency associated with end stage renal disease (Di Cerbo et al., 2013; Wong et al., 2014), renal transplant (Ahmad and Bromberg, 2016), chemotherapy (Wang et al., 2016), or antibiotic therapy (Kujawa-Szewieczek et al., 2015).

Based on extensive in vitro, animal and human data on the role of probiotics in selective management of different metabolites associated with disease progression in humans, we can safely proceed to develop therapeutic products based on selective probiotics and prebiotics. The use of prebiotics and probiotics for the prevention and treatment in several diseases including, pediatric and adult antibiotic-associated diarrhea (Johnston et al., 2016) *Clostridium difficile* infections (McFarland et al., 2016), vaginal health (Reid, 2012; Al-Ghazzewi, 2016) and inflammatory bowel diseases (Sales-Campos et al., 2015) has become widely accepted. While the worldwide burden of infectious diseases has gone down over the years, there is a steep rise in non-communicable diseases (NCDs) such as diabetes, cardiovascular disease, hypertension, and cancer (Prasad et al., 2015). The common denominator among various NCDs is lifestyle-associated rise in obesity leading to metabolic disturbances and inflammation (Lim et al., 2010; Mozaffarian et al., 2014). Alterations in gut microbiota have been suggested as one of the factors in the development of systemic inflammation and metabolic disorders (Hur and Lee, 2015). Dysbiosis or an unhealthy imbalance in the gut microbiota may lead to increased adiposity, β-cell dysfunction, metabolic endotoxemia, systemic inflammation, and oxidative stress: the common features to most NCDs (Lim et al., 2010; Mozaffarian et al., 2014; Prasad et al., 2015). Therefore, it is not unreasonable to suggest that maintenance of healthy gut microbiota may play a preventive role in NCDs (Tomaro-Duchesneau et al., 2015).

To bring this hope to reality, an array of research is needed to improve old technologies and develop new ones related to probiotic production, delivery, storage and stability. There is need for continued research to improve technology for industrial scale production of probiotics while maintaining the stress tolerance during the production, viability and genetic fidelity of the product. There is also a need to develop a better storage milieu to increase viability and functionality of probiotics under diverse storage conditions. The development of technologies aimed at improving the delayed release and survival of probiotics as they transit through the harsh gastrointestinal environment will greatly enhance their efficacy. If probiotics were to stand on the forefront of health management through better nutrition, its applicability must move beyond pills/capsules and dairy products. Therefore, there is an enhanced industrial interest in incorporating probiotics into other foods (juices, drinks, candy bars). This brings new research challenges that must be addressed in concert with specific product manufacturing technology.

In principle, to date there are few real concerns associated with the use probiotics for health maintenance. This is not to say that we will not come across unforeseen concerns in future when probiotic use becomes common. However, the real concerns of today with the use of probiotics reside with adherence to label claims (Patrone et al., 2016), packaging issues (O’Brien et al., 2016) and production conditions (Cinque et al., 2016). Most of these issues could be easily resolved with stricter production, storage, quality control guidelines and their enforcement.

**CONFLICT OF INTEREST:** None declared

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