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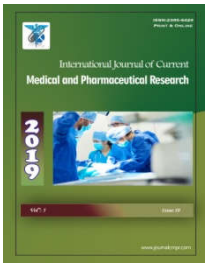

BUTTERMILK AS A POSSIBLE GLYCOTOXINS' ELIMINATOR: A REVIEW

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ABSTRACT

Glycotoxins or advanced glycation end products (AGEs) are coming under the limelight of research field now-a-days. These glycotoxins when get excessively produced in the body; are posing a risk factor for many metabolic disorders like diabetes, cardiac disorders and cancers and are also responsible for premature aging and related diseases like cataract, Alzheimer's disease etc. Researchers have proven that buttermilk which acquires a prime importance in Ayurveda has the potential to eliminate or significantly inactivate these system produced glycotoxins. This review provides here with some noteworthy research results which prove the above statement significantly.

INTRODUCTION

Ancient Indian wisdom, Ayurveda, considers many foods as wellbeing ornamental but among all those, this ancient medical system considers buttermilk as an elixir of life. Although this has been penned down eons before, today there are many researches ongoing as well which are proving the benefits of buttermilk to the human race. Buttermilk is not only advised in minor medical conditions like regurgitation and heartburn etc but it is now finding prime importance in the treatment of certain chronic and lifestyle metabolic disorders like hemorrhoids, ulcers, diabetes, coronary vascular disorders and some forms of neoplasm as well.

In Ayurveda, vast details about types, formulations and properties of buttermilk have been discussed. Modern nutritional findings along with classic texts of Ayurveda suggest the importance of buttermilk as an immune enhancer and that can be used as a promising treatment of gastrointestinal diseases. Similarly novel research findings are also suggesting the use of buttermilk as a glycotoxins inhibitor. Glycotoxins prove harmful when the production rate does not match with their clearance rate; resulting in metabolic disorders. Approximately 10% of the glycotoxins received by food are absorbed in the intestines. One third of the glycotoxins absorbed in the intestines are excreted by the kidneys in 48 hours. The remaining two third are kept in the tissues and accumulate (Kutlu T, 2016). Accumulated glycotoxins exert oxidative stress primarily on kidneys and liver (Smedsrod B *et al*, 1997, Matsumoto K *et al*, 2000).

Hence the endeavor behind writing this review article revolves around an effectiveness of excellent and economical elixir, buttermilk, on glycotoxins inhibition and thus resultant oxidative stress eliminator.

Buttermilk as an Exceptional Dairy Product

Buttermilk is an excellent probiotic. According to Ayurveda, buttermilk is a liquid obtained after churning of curd with water in the proportion of 1:4 respectively. Conventionally, buttermilk is the thin liquid left after preparation of butter. Buttermilk ideally should be devoid of fat content, should not be too thick or too thin in consistency and should be slightly sweet, sour and salty in taste (Patil D *et al*, 2017).

The health benefits of buttermilk have been evidenced by many studies. Clinical trials studying the effects of buttermilk on various diseases (e.g., cholesterol reduction, blood pressure reduction, antiviral effects, and anticancer) have showed positive effects.

Lactose intolerance or inability to digest lactose in adults is common worldwide. People with lactose intolerance are not able to consume whole milk as consumption may cause abdominal pain, bloating and diarrhea, and flatulence. Inability to digest lactose in adults occurs due to the absence or presence of lactase in low levels in small intestine. However, the population suffering from lactose intolerance can consume buttermilk as an alternative for whole milk. The microflora present in buttermilk has the ability to metabolize lactose. The metabolic activity of microbes converts lactose in lactic acid, which is easy to digest. Additionally, buttermilk also plays an

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assistive role in the removal of undesired stomach acid (which causes indigestion and heartburn) by creating a layer on the lining of the stomach and moving the acid through esophagus. Moreover, the interaction of buttermilk with resveratrol has been shown to be helpful in the delivery of this component (Ye *et al*. 2013). In fact, the binding ability of whole buttermilk with resveratrol or a complex formulation enhances the aqueous solubility of resveratrol, which is quite helpful in the delivery of this component in system via the natural route. Further, it has also been suggested that hydrolyzed proteins of buttermilk are a rich source of natural antioxidants (Conway *et al*. 2013).

Turmeric is good source of phenolic components, for example, curcuminoids (curcumin, demethoxycurcumin, and bisdemethoxycurcumin), which have anti-inflammatory and antioxidant activities and other properties of clinical importance. Sometimes, poor stability of these phenolic components in foodstuffs discourages their potential health attributes. However, it has been seen that buttermilk has a good capability to stabilize these phenolic components compared to buffers. So, buttermilk can be used to deliver these turmeric components in the system to impart health benefits (Fu *et al*. 2014).

Further, it has been observed that consumption of cultured buttermilk can decrease the chances of bladder cancer (Larsson *et al*. 2008). It has also been suggested that buttermilk intake can reduce cholesterol levels by inhibiting the assimilation of cholesterol in the intestinal tract (Conway *et al*. 2013a).

Consumption of buttermilk can reduce blood pressure in moderately hypercholesterolemic individuals. It was seen that arterial blood pressure and systolic blood pressure get reduced with continuous buttermilk consumption. The concentration of angiotensin-I converting enzyme also decreased in plasma, while levels of angiotensin-II and aldosterone remained unchanged (Conwey *et al* 2014a). In another study, Fuller *et al*. (2013) showed anti-rotavirus activity using the milk fat globule membrane obtained from buttermilk. The routine consumption of buttermilk leads to a decrease in weight. Individuals can replace whole milk with buttermilk to gain health attributes (Conway *et al*. 2014b).

Many workers are investigating to find out the role of buttermilk as health drink; for example, the functions of buttermilk phospholipids have been related with many health benefits. However, the validation of buttermilk benefits (i.e., anticancerous and anticholestrolic activities) is needed in detail.

Latest evidences show that buttermilk has the ability to inactivate advanced glycation end products (AGEs).

Glycation and Glycotoxins

The non-enzymatic and spontaneous reaction of amino groups of proteins, nucleic acids, and lipids with the other reducing sugars is called glycation (Kutlu T, 2016). Brown substances formed when food is cooked glamorize the color, odor, and taste of food, and render it more attractive. This fact was defined in 1912 by Louis Camille Maillard and is also called the Maillard reaction. During the Maillard reaction, harmful substances called Maillard reaction products emerge. These substances are currently called advanced glycation end products (AGEs) (Kaanane A & Labuza T 1989, O'Brien J & Morrissey P 1989). The primary products in the form of ketoamines, which are formed by way of glycation, are not stable and are transformed into AGEs by disintegrating via oxidative and non-oxidative mechanisms. Glycation products formed during smoking and cooking food at high temperatures are received exogenously and are called glycotoxins (Palimeri S *et al* 2015, Cerami C *et al* 1997).

Approximately 10% of the glycotoxins received by food are absorbed in the intestines. One third of the glycotoxins absorbed in the intestines are excreted by the kidneys in 48 hours. The remaining 2/3 are kept in the tissues and accumulate. The kidneys are the most important organs in excretion of glycotoxins. A portion of the glycotoxins filtered in the glomeruli is disintegrated in the tubuli and the remainder is excreted in urine. Renal diseases lead to a reduction in the excretion of glycotoxins in the urine and an increase in glycotoxins in plasma and tissues. It has been reported that the accumulated glycotoxins may have harmful effects on renal function and especially on the proximal tubuli, which are involved in glycotoxin catabolism (Koschinsky T *et al* 1997, Gugliucci A *et al* 1996). The liver is another organ involved in glycotoxin metabolism and elimination. It performs this action through receptors found in the hepatic sinusoids and Kupffer cells. It has been shown in mouse experiments that albumin-bound glycotoxins given intravenously accumulate rapidly in the liver and this accumulation occurs in endothelial cells with a rate of 60%, in the Kupffer cells at 25%, and in the parenchymal cells at 10-15%. In addition, the liver also contributes to the production of inflammatory molecules, which are formed as a result of oxidative stress caused by glycotoxins (Smedsrod B *et al* 1997, Matsumoto K *et al* 2000).

Glycation is the most important reason of spontaneous damage in proteins. Proteins can be repaired by elimination of protein-bound fructosamine and other ketoamines by fructosamine-3-kinase and similar enzymes. Protein glycation is an inevitable mechanism despite enzymatic repair mechanisms and glycotoxins continue to increase in conditions including diabetes as a result of increased glucose concentration. Proteins that have been exposed to glycation lead to an inflammatory response by way of AGE receptors (RAGE) and cause gene activation. As a result, various inflammatory diseases develop. It is currently thought that glycotoxins are involved in the pathogenesis of a great number of diseases including diabetes complications, renal failure, hepatic diseases, neurodegenerative diseases, eye diseases, and cancer (Singh R *et al* 2000, Poulsen M *et al* 2013).

Physiological Effects of AGEs

AGEs are generated in vivo as a normal consequence of metabolism, but their formation is accelerated under conditions where blood glucose is chronically elevated such as poorly controlled diabetes [Brownlee, 2001]. AGE formation is also increased in the presence of oxidative stress, which is frequently observed in individuals with the metabolic syndrome [Folli *et al*, 2011, Kotani and Sakane, 2012]. Overproduction of reactive oxygen species (ROS) can result in maladaptive responses including interruption of cellular glycolysis, which can generate highly reactive dicarbonyl compounds capable of rapid AGE formation [Thornalley P, 2005].

Excessive AGE accumulation can lead to several pathophysiological consequences. AGE-modification of

proteins results in changes in structure and/or function. For example, the AGE-modification of extracellular collagen reduces its elasticity and solubility, and results in increased stiffness, disturbed cellular adhesion and reduced turnover contributing to basement membrane thickening [Avery N & Bailey A, 2006]. Intracellularly, AGE-modification of mitochondrial proteins is associated with suppression in the activity of respiratory chain enzymes and overproduction of ROS [Rosca *et al*, 2005, Coughlan *et al*, 2009]. Indeed, glycated proteins provide stable active sites for catalysing the formation of free radicals [Yim M *et al*, 2001]. Finally, AGEs are able to bind and activate a range of receptors, which then trigger a downstream cascade of pathogenic mediators. Interaction of AGEs with the Receptor for AGEs (RAGE) promotes activation of the transcription factor nuclear factor kappa-B (NF-κB), with subsequent up regulation of chemokines, such as MCP-1 and pro-fibrogenic mediators such as TGFβ in addition to pro-inflammatory cytokines which are known to be involved in thrombogenesis, vascular inflammation and pathological angiogenesis. These RAGE-mediated events contribute to many of the long-term complications of diabetes [Schmidt A *et al*, 1995]. AGE/RAGE ligation also promotes overproduction of ROS which can then activate NF-κB [Morita M *et al*, 2013], a key driver of inflammation.

More recently, AGEs have been implicated in the pathogenesis of both type 1 and type 2 diabetes. Several studies have shown that AGEs are associated with insulin resistance [Tahara N *et al*, 2012, Tan K *et al*, 2011], and can induce low-grade inflammation [Uribarri J *et al*, 2005] and pancreatic beta cell dysfunction [Fiory F *et al*, 2011, Coughlan M *et al*, 2011].

In contrast to endogenous AGE formation, AGEs are also absorbed by the body from exogenous sources such as cigarette smoke and through consumption of processed foods [Birlouez-Aragon I *et al*, 2010]. Since AGEs are generated within foodstuffs upon heating and food processing, it is increasingly recognized that the modern diet is replete with AGEs [Tessier F *et al*, 2012]. AGE-restricted diets can arrest the development of type 2 diabetes in animal models [Sandu O *et al*, 2005]. A recent study found that excess consumption of AGE-precursors in mice over several generations led to the development of insulin resistance [Cai W *et al*, 2012]. Human trials have found that dietary AGE restriction can improve insulin sensitivity [Uribarri J *et al*, 2011, Mark A *et al*, 2014] and decrease markers of oxidative stress [Luevano-Contreras C *et al*, 2013] or inflammation [Harcourt B *et al*, 2011]. Further studies are required to confirm the long-term benefits of dietary AGE-restriction in humans [Kellow N *et al*, 2013]. However, simple, safe and effective interventions which prevent or minimize excessive AGE accumulation and subsequent AGE-related pathology in people with diabetes and/or in those at risk of developing the condition are warranted [Kellow N *et al*, 2014].

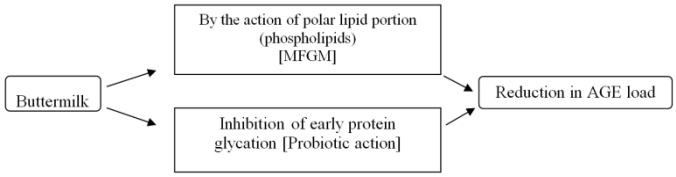
Effects of Buttermilk on Glycotoxins

AGEs originating from diet have a significant contribution to the AGEs body pool and therefore dietary interventions aiming at reducing AGEs load are believed to exert health promoting effects (Stirban and Tschope 2015).

As said earlier, buttermilk is an excellent probiotic. Probiotics can induce changes in the gut microbiota, stabilize microbial communities and exert beneficial effects on the health of the host. Some studies have also demonstrated an effect of the probiotics on the early glycation since the HbA1c content was decreased after a long-term exposure to *Lactobacillus* strains. Similar results were reported in clinical trials where volunteers consumed probiotics over a period of four to eight weeks [Ejtahed H *et al* 2012, Moroti C *et al* 2012]. These clinical studies showed a remarkable decrease in blood sugar level, oxidative stress and early glycation (HbA1c concentration) (Guilbaud A *et al* 2016). In a similar research carried out by Patil *et al* in 2018, it was interesting to note that while aminoguanidine could inhibit protein glycation significantly, use of probiotics also demonstrated a similar effect points to the importance of gut microbiota in promoting positive changes. Thus their study raised the possibility of prevention of establishment of diabetes and its progression through use of protein glycation inhibitors and probiotics.

Buttermilk, the co-product of butter making, is particularly rich in MFGM (milk fat globule membrane) components and can play a possible role in glycotoxins elimination. The minor components of the milk fat globule membrane have been associated with various health benefits. There is much evidence in support of hypoglycemic, cholesterol-lowering, anti-inflammatory, chemotherapeutic and anti-neurodegenerative effects of MFGM lipids, mainly through the action of the polar lipid portion (i.e., phospholipids). Not only lipids, but also minor proteins associated with the MFGM are thought to be important bioactive components (Conway *et al*., 2014).

Following figure summarizes the possible action of buttermilk on AGE elimination.



It is thought that certain dietary AGEs are largely undigested by human gut enzymes and eventually enter the colon, where they may act as a growth substrate for detrimental bacteria such as some *Clostridium* and Bacteroides species [Mills D *et al*, 2008]. Therefore it is conceivable that individuals who consume highly processed diets (which contain large quantities of AGEs) may adversely alter their colonic microbial composition, potentially enhancing their risk for the development of metabolic diseases such as obesity and type 2 diabetes [Nakamura Y & Omaye S, 2012].

Therapeutic manipulation of the gut microbiota and restoration of normobiosis could potentially reduce circulating AGE levels and improve the metabolic health of individuals at risk for the development of type 2 diabetes. Regular consumption of prebiotics to promote the growth of beneficial gut bacterial flora is one such avenue currently under investigation. Supplementation of the human diet with prebiotic fructans such as inulin or fructo-oligosaccharides along with probiotics alters the bacterial composition of the large intestine by favouring the selective proliferation of beneficial lactic acid-producing species such as *Bifidobacteria* and *Lactobacilli*. Prebiotic-stimulated increases in intestinal *Bifidobacterium* species have been shown to attenuate the production of ROS and markers of inflammation in individuals consuming high fat diets [Delzenne N *et al*, 2011].

CONCLUDING REMARKS

From the detailed appraisal of findings of the researches, it is well understood that buttermilk could serve as a fine glycotoxins eliminator via stated possible mechanisms. This reference can be found in some classical Ayurveda texts but its mechanism on the target substance is yet to be researched thoroughly and requires extensive biochemical analysis. It is also essential to understand whether buttermilk can eliminate exogenously produced AGEs as efficiently as endogenously produced AGEs. A much comprehensive *in vivo* and *in vitro* research is needed in this focus to draw promising conclusions.

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