Potato Glycoalkaloids

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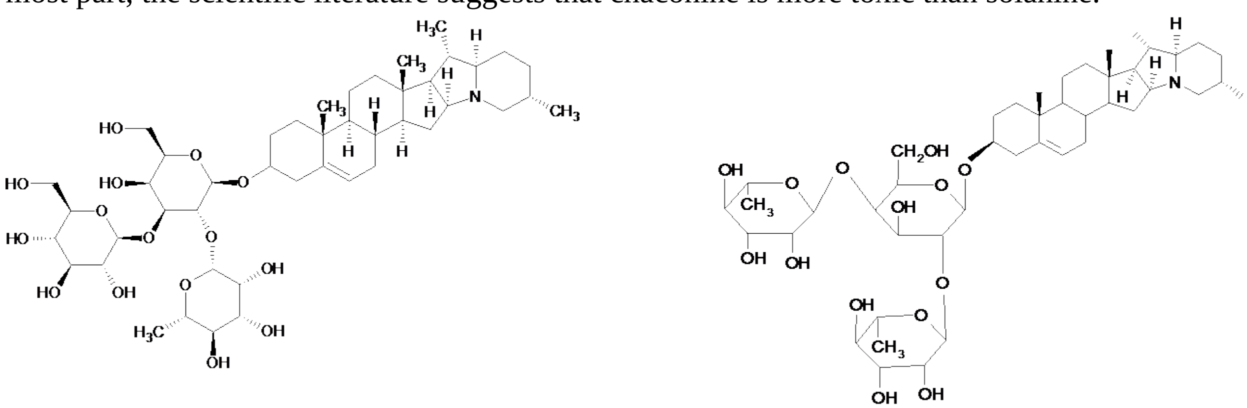
Introduction

This report will focus on the importance of glycoalkaloids from a potato industry perspective and summarize a talk given at the 2016 Washington-Oregon Potato Conference. Other than a very brief description of the chemistry of glycoalkaloids, the article will address “real world” consequences resulting from the presence of toxic glycoalkaloids in potatoes. As this article will discuss, it’s possible that we don’t know as much about glycoalkaloids as we thought we did and that they might not be entirely the villains we thought they are.

What are glycoalkaloids?

Glycoalkaloids are natural chemicals found in potatoes and other solanaceous plants that can be toxic if present in too high a concentration. In North America there is a general voluntary guideline that glycoalkaloids in potatoes must be below 20 mg/100g fresh weight. Amounts reported in other plants vary (eggplants: 6.3-20.5 mg/100g; peppers: <10 mg/100g; and tomato: <0.5mg/100g FW ripe fruit; up to 339 in green wild species fruit). Their role in plants is to contribute to pest and pathogen resistance. Glycoalkaloids (**GAs**), are steroidal alkaloids comprised of a heterocyclic nitrogen, and a C_{27} steroid conjugated to a sugar moiety, most commonly a tri- or tetrasaccharide. Most potato GAs are solanidanes such as solanine and chaconine (**Fig. 1**). Less common in the cultivars are spirosolanes such as tomatine. Solanine and chaconine typically comprise upwards of 90% of the total GA content in potato cultivars, although estimates have been made that the potato family contains over 90 different GAs. For the most part, the scientific literature suggests that chaconine is more toxic than solanine.



Solanine Chaconine

Figure 1: Solanine and chaconine, the two major glycoalkaloids in potato cultivars.

How do glycoalkaloids impact the Industry?

A) Negative aspects of glycoalkaloids. The primary reason the potato industry is interested in glycoalkaloids is because they can be toxic to humans if present in high concentrations. Also important is that glycoalkaloids influence potato flavor, and they influence the ability of the plant to resist pests and pathogens.

Issue: From a dietary viewpoint, GAs are regarded as anti-nutritive compounds that if ingested in high amounts can cause a burning sensation in the mouth and throat, fatigue, vomiting, cramping, hallucinations, nausea, rapid pulse and other ill effects. These effects are mainly a consequence of GA disruption of cell membranes and inhibition of cholinesterase activity. Estimates vary about the amount of GAs needed to be ingested to have toxic effects, with 1-5 mg/kg of body weight the commonly suggested range. GAs are found in much higher concentrations in leaves, sprouts and fruit than in tubers, and in higher amounts in the skin versus flesh. GA concentrations approaching 18 grams/kg FW have been reported in sprouts. In 1983 in Alberta, Canada 61 school children became sick and recovered within 3 hours shortly after eating baked potatoes with a green tinge and bitter taste that contained 49 mg/100g FW of GAs.

Issue: Exposure of potatoes to the sun causes greening and results in increased amounts of glycoalkaloids. Red and blue wavelengths seem to induce the most GA expression in tubers and yellow the least. Sodium lamps induce greater amounts than mercury. Some markets, including in Asia, view greening as a serious defect, associate it with toxicity and can reject shipments due to small amounts of greening. Some report that 14-27% of some shipments can be rejected due to greening. Whether some cultivars are more prone than others to light-induced increases in glycoalkaloids is not known. Limited data suggested Kerr’s Pink was more prone to greening than Desiree and Sabina more than Bintje. Identification of cultivars that are resistant to both greening and the associated increase in glycoalkaloids would be a significant advance. Also not well-understood is whether greening always results in an increase in glycoalkaloids, or if greening can occur without an increase in glycoalkaloids, or whether tubers can be exposed to light and glycoalkaloids increase but without any greening. Research is underway in these areas.

Issue: In our risk adverse modern society, there is increasing concern that breeding lines in the 10-20 mg/100g FW (i.e. historically accepted and safe amounts) might be unsuitable because of worries that their GAs *might* possibly increase above 20 mg/100g FW in response to environmental triggers, as happened with cultivar CalRed a decade ago. This fear exists because the environmental, physiological and genetic regulation of GLK levels in tubers is not sufficiently understood. Concern about glycoalkaloids can cause breeding programs to try to breed for lines as low as possible, a strategy that may have some drawbacks (**Table 1**). If 10-20 mg is precluded as an acceptable range, this can slow new cultivar development by impeding use of primitive germplasm with highly desirable traits because the progeny of such crosses can have higher amounts of glycoalkaloids than the typical cultivar. Moreover, unnecessarily low glycoalkaloid amounts can negatively impact pest/pathogen resistance and potentially negatively impact flavor if glycoalkaloid levels are limited to levels below 10 mg/100 g FW. The primary function of GAs in potatoes is to protect the plant against pathogens and pests, so reducing GA amounts more than necessary for human safety will result in plants with less disease/pest resistance. Potatoes increase their GAs in response to disease/pests, but the extent of such increases vary based on the specific disease and the specific cultivar, and are poorly understood. So these represent a wildcard that could cause unanticipated increases in GAs. Furthermore, as described below, unnecessarily low glycoalkaloid amounts *may* not be desirable from a health standpoint.

Table 1. Possible undesirable effects of potatoes with unnecessarily low amounts of glycoalkaloids.

1	More difficult to incorporate wild germplasm into breeding programs
2	Unnecessary elimination of superior new cultivars by excluding the 10-20 mg/100 g range
3	Can decrease pest/pathogen resistance
4	Can potentially affect flavor
5	Will reduce dietary intake. Is this good or bad?

Issue: Environment and management can cause glycoalkaloid amounts to spike. It is largely fear of the potential for such spikes that can influence breeders to favor breeding lines that have below 10 mg/100 g FW GA. The main concern about the potential for GA spikes is that such spikes are not entirely predictable, nor is it well understood whether some lines are more prone to spikes than others. Over the decades, there are have times when glycoalkaloid amounts spiked very high, even for a cultivar like Russet Burbank where a range of 4-39 mg/100 g FW was reported in one study, and another found 80 mg/100 g FW in Burbank potatoes exposed to sun in the field. The chipping cultivar Lenape was withdrawn from production in North America after a range of 16-65 mg/100 g FW was found in a 1970 survey, in which potatoes from Parma, ID contained 65 mg/100 g FW. The Parma levels may have been associated with a killing frost two weeks before harvest. Levels of 4-35 mg have been reported for Kennebec and 2-21 mg for Katahdin. In a Canadian study, GA levels in Burbank tripled after 6-8 hours exposure to sunlight near freezing temperatures. GAs in the Swedish cultivar Magnum Bonum were found to vary between 6-67 mg/100 g FW.

Injury can elevate amounts as much or more than greening. A combination of cold, wet soils and clouds may stimulate an increase in GAs. Magnesium is reported to increase GAs, whereas mixed results have been found with nitrogen amounts. Inconsistent findings are also reported with vine killing. Based on limited, older data, one paper suggested spikes in glycoalkaloids may be more common in cultivars with GA averages greater than 10 mg/100 g FW, but like much of the older GA literature, the data is not conclusive.

Because of these potential environmental influences on GAs, a concern for new cultivars is that their GA levels, established as acceptable over years of evaluation during the breeding process over multiple states, when grown on an even larger scale could nevertheless inexplicably spike to an unacceptable amount in a particular year or location for unknown and unpredictable environmental causes. This concern would be reduced if we could better predict the effect of environment on any given cultivar. Increased understanding of the biochemical and molecular mechanisms leading to increased GA synthesis in tubers might increase our ability to predict how a given cultivar is going to respond to a range of environments.

Issue: The market for baby potatoes is growing and these potatoes are valued by consumers for their taste, appearance and novelty. They also have higher amounts of many phytonutrients than at maturity and appeal to atypical potato buyers. However, baby potatoes have higher amounts of GAs than at maturity and this can be a bottleneck for bringing new consumer-oriented baby potato cultivars to the market. Moreover, we've found baby potatoes from numerous genotypes had amounts beyond expectations.

B) Positive aspects of glycoalkaloids.

For decades it has been mantra that GAs are categorically undesirable in potatoes. A leading authority on GAs in the 70s and 80s (Sinden) wrote: "Glycoalkaloids have no known positive role in human nutrition; the known and suggested effects of even small quantities of these natural toxicants are all negative". However, this longstanding perspective may be simplistic and based on attitudes arrived at before some of the benefits of glycoalkaloids were known. As discussed further below, numerous recent studies show health-promoting effects of glycoalkaloids.

Obviously, potatoes must contain GA amounts below the threshold that have any ill effects in humans, but recent research showing health benefits may change how we think about GAs. If one considers a compound a toxin, they are going to have a very different attitude about the compound than if they thought it was a medicine or a compound with some beneficial, desirable properties. For example, medicines are typically toxic if taken at too high a dosage, but people do not have a negative attitude about medicines. Perhaps an analagous situation exists with glycoalkaloids in which people perceive them strictly as toxins with no redeeming qualities.

1) Health-promoting effects:

There are too many studies to mention in this report, so the information below only covers a small portion of the evidence for health-promoting effects of glycoalkaloids. Recent studies convincingly show GAs have anti-cancer properties, both *in vitro* and *in vivo*. The most frequent cause of cancer-related death is lung cancer, in part because of its propensity to metastasize before it is diagnosed. Using a human lung cancer cell line, α-chaconine reduced metastasis and may allow new chemotherapeutic approaches (Shih et al., 2007). A separate study showed that solamargine, a GA found in some potatoes, increased the susceptibility of two types of human lung cancer cell lines to anticancer drugs (Liang et al., 2008). Solasodine, may protect against skin cancer (Cham, 1994). GAs including tomatine, solanine and chaconine inhibited growth of human colon and liver cancer cells in cell culture assays with a potency similar to the anticancer drug Adriamycin (Friedman et al., 2005; Lee et al., 2004). GA anticancer effects were also seen in assays using cervical, lymphoma and stomach cancer cells. Treatments using two or more GAs suggested synergistic and additive effects (Friedman et al., 2005). Solamargine enhanced susceptibility of breast cancer cells to anti-cancer drugs, while various solanidines exhibited cytotoxicity towards multidrug resistant cancer cell lines. (Shiu et al., 2009; Zupko et al., 2014). Micromolar concentrations of solamargine triggered apoptosis in human leukemia cells and squamous cell carcinoma and other solasodines also had efficacy (Cui et al., 2012; Sun et al., 2011). Chaconine showed efficacy in cell studies against stomach, colon, liver and cervical cancer (Friedman, 2015) and prostate cancer (Reddivari et al., 2010).

Solanine, a major GA in potatoes, showed efficacy against various cancers, including pancreatic cancer, not only *in vitro* in human pancreatic cancer cells, but in mice where it suppressed proliferation, angiogenesis and metastasis (Lv et al., 2014). Creams containing glycoalkaloids showed efficacy against skin cancer in mice and in humans, while a clinical trial with 86 subjects showed low doses of solasodines had 100% efficacy (Cham et al., 1991). A feeding study using rainbow trout reported reduced tumor incidence in tomatine fed trout (Friedman et al., 2007). Tomatine suppressed growth of prostate cancer cells in mice (Lee et al., 2013). Tomatidine has potential as a chemosensitizing agent, increasing the effectiveness of cancer chemotherapy by inhibiting multidrug resistance in human cancer cells (Lavie et al., 2001).

In addition to anticancer efficacy, GAs may boost the immune response. Mice treated with solasodines underwent cancer remission, and a majority of the mice remained resistant to subsequent injection with terminal doses of cancer cells, suggesting glycoalkaloids prime the immune system for long-term cancer protection (Cham and Chase, 2012). Mice fed GAs were more resistance to infection by Salmonella (Gubarev et al., 1998) and tomatine improved the mice immune response to vaccines (Rajananthanan et al., 1999). GAs inactivate several types of herpes viruses (Chataing et al., 1997). Some GAs showed antimalarial activity in vivo (Chen et al., 2010) and were lethal against parasitic flatworms (Miranda et al., 2012).

2) Plant disease and pest resistance

The role of glycoalkaloids in potatoes is to contribute to the plant's ability to resist plants and pathogens. In most cases it is unlikely that GAs by themselves determine whether the plant will be resistant or not, but it is more likely that they are part of the overall defense arsenal used by plants.

A study of the feeding behavior of specialist and generalist insect herbivores between domesticated potato and the wild species *S. commersonii* concluded domestication altered the defensive capacity of *S. tuberosum*, and that the altered GA profiles between the two explained the different feeding behavior of the herbivores. A comparison of glycoalkaloid profiles between domesticated potatoes susceptible to Colorado potato beetle and six resistant potato wild species observed a correlation between resistance and glycoalkaloids with a tetrose side chain such as tomatine and dehydrocommersonine. GAs have also been shown to have nematicidal activity and be effective against wireworms and leafhoppers. Glycoalkaloids are also effective against pathogens, for example inhibiting the growth of Early Blight in culture.

3) Taste

High concentrations of glycoalkaloids lead to a bitter taste, but the data is inconsistent about the threshold for bitterness. Some suggest that amounts as low as 11 mg/100 g FW lead to a bitter taste, whereas others suggested the threshold is above 25 mg/100 g FW. Chaconine was more bitter than solanine in a small study using purified glycoalkaloids. While the potential of GAs to contribute to bitterness are well known, less well known are findings that at lower levels GAs may positively affect flavor.

Effect of cooking and processing on GAs

When trying to determine the optimal range of glycoalkaloids in potatoes and what is a safe amount, one must consider the effect of cooking on GAs. Historically, cooking has been thought to have little effect on glycoalkaloids, as was consistently shown in multiple studies. Studies with purified glycoalkaloids found GAs to be very resistant to heating below about 450 °F. However, more recent studies show cooking and processing can markedly decrease the amount of GA present in the cooked product. Peeling was shown to reduce GA amounts by 20-70%. Leaching also decreases the amount. One study of dehydrated potatoes found 70% of the GAs were removed by peeling and 29% during blanching. Similarly, recent studies of French fries and potato chips have reported over an 80% reduction in GAs compared to the raw product. Data such as these may be particularly relevant to keep in mind when assessing the fate of breeding lines that are in the 10-20 mg/100g FW.

Conclusions

Recent discoveries have potential to alter the perception of glycoalkaloids. The findings of health-promoting effects may ameliorate the view that glycoalkaloids are just toxins and entirely undesirable. Are low doses of GAs dietarily desirable? If so, then potatoes, eggplants and peppers may be unique suppliers of these in the diet. If this were true, then reducing them to unnecessarily low amounts could actually be dietarily undesirable. More information is needed in this area.

Multiple knowledge gaps remain in other areas. Despite a great deal of study on glycoalkaloids over the decades, there are a lot of conflicting reports published and some of the more widely held assumptions about glycoalkaloids may not be as ironclad as thought. One major industry concern is the ability to trust the stability of a cultivar's GA content regardless of location or year. More detailed knowledge of environmental factors that increase GAs and the mechanisms that control the amount of GAs in tubers would increase confidence that a given cultivar will not exceed expected amounts, which would decrease the concern of unanticipated increases during growing and handling. Identifying the regulatory mechanisms that control GA amounts would allow breeders to work with a wider range of germplasm, facilitating enhancement of a broad range of traits, while concurrently developing cultivars with optimal amounts of glycoalkaloids that are safe for consumption, but at the same time don't require increased pesticide use due to decreased disease and pest resistance.

Also not clear is to what extent cultivars can be developed that have high amounts of GAs in the foliage for pest/pathogen resistance, but low amounts in tubers. Identifying best practices to reduce greening or cultivars that are less prone to greening will protect important export markets that consider greening a major defect. Additional stakeholder driven applied research on the effect of various light sources and spectrum on greening and GA development are needed, as is information about whether greening and increases in GA content are always linked.

Collectively, such information would help ensure continued food safety, protect growing markets and produce updated best practices and guidelines for growers, processors, storage sheds, and retailers.