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REVIEWS

Potato Glycoalkaloids and Metabolites: Roles in the Plant and in the Diet

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Potatoes, members of the Solanaceae plant family, serve as major, inexpensive low-fat food sources providing energy (starch), high-quality protein, fiber, and vitamins. Potatoes also produce biologically active secondary metabolites, which may have both adverse and beneficial effects in the diet. These include glycoalkaloids, calystegine alkaloids, protease inhibitors, lectins, phenolic compounds, and chlorophyll. Because glycoalkaloids are reported to be involved in host-plant resistance and to have a variety of adverse as well as beneficial effects in cells, animals, and humans, a need exists to develop a clearer understanding of their roles both in the plant and in the diet. To contribute to this effort, this integrated review presents data on the (a) history of glycoalkaloids; (b) glycoalkaloid content in different parts of the potato plant, in processed potato products, and in wild, transgenic, and organic potatoes; (c) biosynthesis, inheritance, plant molecular biology, and glycoalkaloid−plant phytopathogen relationships; (d) dietary significance with special focus on the chemistry, analysis, and nutritional quality of low-glycoalkaloid potato protein; (e) pharmacology and toxicology of the potato glycoalkaloids comprising α-chaconine and α-solanine and their hydrolysis products (metabolites); (f) anticarcinogenic and other beneficial effects; and (g) possible dietary consequences of concurrent consumption of glycoalkaloids and other biologically active compounds present in fresh and processed potatoes. An enhanced understanding of the multiple and overlapping aspects of glycoalkaloids in the plant and in the diet will benefit producers and consumers of potatoes.

Keywords: Glycoalkaloids; α-chaconine; α-solanine; chemistry; analysis; biosynthesis; host-plant resistance; pharmacology; toxicology; beneficial effects; organic potatoes; transgenic potatoes; potato protein; food processing; food safety; human health

INTRODUCTION

The Solanaceae plant family contains members that are relevant to human nutrition and health. These include capsicum (peppers), eggplant, tomato, and potato as well as black nightshade and jimson weed seeds and tobacco. These plants produce beneficial as well as potentially toxic compounds, both during growth and during postharvest marketing. These compounds include alkaloids and glycoalkaloids. Glycoalkaloids are secondary plant metabolites that at appropriate levels may be toxic to bacteria, fungi, viruses, insects, animals, and humans. The potential human toxicity of glycoalkaloids has led to the establishment of guidelines limiting the glycoalkaloid content of new cultivars before they can be released for commercial use. Following harvest, the glycoalkaloid content can increase during storage and transportation and under the influence of light, heat, cutting, slicing, sprouting, and exposure to phytopathogens.

The main objective of this review is to unify widely scattered information on the multifaceted aspects of glycoalkaloid chemistry and their roles in the plant and in the diet. The essay interprets and extends information in previous reviews on potato and tomato glycoalkaloids (*1*, *2*). Although glycoalkaloids are perceived as potentially toxic, studies during the past 10 years suggest that they may also possess beneficial effects, depending on dose and conditions of use. Moreover, in addition to glycoalkaloids, potatoes contain other biologically active compounds (calystegine alkaloids, antioxidative phenolic compounds, chlorophyll, protease inhibitors, lectins, vitamins) as well as processing-induced browning compounds and acrylamide. These may affect the dietary roles of glycoalkaloids. We are challenged to define the conditions under which these dietary ingredients enhance or suppress adverse and beneficial effects

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of glycoalkaloids. Collectively, the available information outlined below may guide further needed efforts to minimize adverse effects and optimize beneficial ones.

HISTORICAL PERSPECTIVE

Commercial potatoes are derived from inbreeding and selection of wild potatoes domesticated in the Andes Mountains of South America (*3*, *4*). Spaniards first transported them to Europe from 1565 to 1570. Wild potatoes (*papas criolas*) are still widely consumed by the indigenous population of South America. The alkaloid solanine, isolated by French scientists from potatoes in the year 1820 (*5*, *6*), was later shown to be a glycoside (*7*). About 100 years later it was shown that solanine is a mixture of two compounds, α-chaconine and α-solanine (*8*). Seminal studies by Kuhn and Löw (*8*−*12*) and by Ripperger and colleagues (*13*, *14*) carried out in Germany beginning in the 1950s clarified the fundamental chemistry of glycoalkaloids. Other important studies include those by Pokrovskii (*15*) in Russia in 1956 and by Orgell ands Vaidya in 1958 (*16*) on the inhibition of cholinesterase; by Heftmann (*17*−*19*) at this laboratory on the biosynthesis; by Rühl (*20*) in Germany and Nishie and colleagues at this laboratory (*21*) on the pharmacology and toxicology; by Sinden and colleagues at the USDA laboratory in Beltsville, MD, on the role of foliar leptine glycoalkaloids in plant resistance (*22*); by Roddick and colleagues in the United Kingdom (*23*, *24*) and by Keukens and colleagues in The Netherlands (*25*−*27*) on the disruption of cell membranes; on the possible teratogenicity in humans in the United Kingdom (*28*−*31*); and by Friedman and collaborators on analysis (*2*, *32*−*45*), activities in frog embryos (*46*−*55*), and suppression of genes that encode enzymes involved in the biosynthesis (*1*, *56*−*61*). Recent findings on the (a) development of ELISA (*42*) and biosensor (*62*) methods; (b) development of low-glycoalkaloid, high-quality potato protein (*63*, *64*); (c) development of improved transgenic (*65*) and organic potatoes (*66*); (d) discovery of calystegine alkaloids in tubers (*35*); (e) effects in humans (*67*); and (f) beneficial effects against human cancer cells (*68*, *69*) and the immune system of rats (*70*, *71*) demonstrate the continuing worldwide interest in glycoalkaloids.

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Structures of Glycoalkaloids. The two major glycoalkaloids in domestic potatoes (*Solanum tuberosum*) are α-chaconine and α-solanine. **Figure 1** shows that α-chaconine is composed of a branched β-chacotriose (bis-α-L-rhamnopyranosyl-β-D-glucopyranose) carbohydrate side chain attached to the 3-OH group of the aglycon solanidine, whereas α-solanine has a branched β-solatriose (α-L-rhamnopyranosyl-β-D-glucopyranosyl-β-galactopyranose) side chain also attached to the 3-OH group of the same aglycon. The trisaccharide chains of both glycoalkaloids can be sequentially cleaved by acid or enzyme hydrolysis to form the aglycon solanidine. **Figure 2** shows the formation of eight hydrolysis products derived by stepwise removal of carbohydrate moieties from the trisaccharide side chains of α-chaconine and α-solanine (*14*, *72a*). Potatoes may contain small amounts of the hydrolysis products β- and γ-chaconines and solanines and solanidine.

Figure 1 also shows two other structural classes of potato glycoalkaloids, the leptines and leptidines, present in the leaves of *Solanum chacoense* but not in the leaves of *Solanum tuberosum*. They are not found in potato tubers. There are two aglycons in this group—leptinidine (23-hydroxysolanidine) and 23-acetylleptinidine. Stereochemically, the 23-OH or 23-OAc group is situated in the axial β-position of the ring. Leptinine I and leptinine II are the respective chacotriose and solatriose glycosides of leptinidine. Leptine I and leptine II are the respective chacotriose and solatriose glycosides of 23-acetylleptinidine.

Table 1. Glycoalkaloid Content of Extracts of Potato Flesh, Peel, and Whole Potatoes(*35*)

	μg/g			
sample (dehydrated powder)	α-chaconine (A)	α-solanine (B)	total (A + B)	ratio (A/B)
Atlantic potato peel	59.4	24.4	83.8	2.43
Atlantic potato flesh	22.6	13.9	36.5	1.63
Russet Narkota potato peel	288	138	425	2.09
Russet Norkota potato flesh	3.7	2.7	6.4	1.37
Dark Red Norland potato peel	859	405	1264	2.12
Dark Red Norland potato flesh	16.0	6.1	22.1	2.62
Snowden potato peel	2414	1112	3526	2.17
Snowden potato flesh	366	226	591	1.62
Russet whole potatoes	65.1	35.0	100	1.86
White whole potatoes	28.2	15.3	43.5	1.84
Benji whole potatoes	70.7	27.6	98.3	2.56
Lenape whole potatoes	413	216	629	1.91

Table 2. Glycoalkaloid Content of Processed Commercial Potato Products (*32*, *319*)

	mg/kg			
processed product	α-chaconine (A)	α-solanine (B)	total (A + B)	ratio (A/B)
French fries, A[a]	0.4	0.4	0.8	1.00
French fries, B[a]	4.2	4.2	8.4	1.00
wedges[a]	23.9	20.1	44.0	1.18
chips, A	13.0	10.5	23.8	1.23
chips, B	31.6	17.6	49.2	1.79
chips, C	58.8	50.2	109.0	1.17
skins, A	38.9	17.4	56.3	2.23
skins, B	44.0	23.6	67.6	1.86
skins, C	116.1	72.3	188.4	1.60
skins, D	119.5	83.5	203.0	1.43
pancake powder, A	20.5	24.1	44.6	0.82
pancake powder, B	24.8	19.4	44.2	1.27

[a] Values are for dehydrated powders. All other values are for original products.

Structure−biological activity relationships of glycoalkaloids and metabolites are described below. Future studies will undoubtedly use molecular modeling to define effects of structural features of glycoalkaloids and metabolites on interactions with cellular receptor sites. These models may make it possible to predict the biological effects of glycoalkaloids and metabolite solely on the basis of their chemical structures. It is relevant to note the Glossman-Mitnik successfully used a chemistry model within Density Functional Theory, called CHIH-DFT, to calculate the molecular structure of solanidine, an important precursor for the synthesis of hormones, as well as of γ-solanine (*72b*,*c*).

Analysis. The complex nature of glycoalkaloid−dietary relationships suggests the need for accurate methods to measure the content of each individual glycoalkaloid and its metabolites in both fresh and processed potatoes as well as in the body fluids such a plasma and tissues such as liver of a consumer. Diverse analytical procedures (*40*) including the following have been used for glycoalkaloids: colorimetry (*73*, *74*), high-performance liquid chromatography (HPLC) (*32*, *34*, *35*, *75*−*80*), gas chromatography (GC) (*81*, *82*), thin layer chromatography

(TLC) (*45*, *83*), mass spectrometry (MS) (*45*, *84*, *85*), enzyme-linked immunosorbent assay (ELISA) (*42*, *86*), and the biosensors (*62*).

HPLC methods are now widely used to determine the concentrations of individual glycoalkaloids of fresh and processed potatoes and different parts of the potato plant such as leaves and sprouts, as well as glycoalkaloid hydrolysis (glycolysis) products. To further improve the HPLC method, we optimized the analysis by systematically evaluating several parameters anticipated to influence the chromatographic separation of known α-chaconine and α-solanine mixtures as well as in extracts of potatoes (*35*). **Figure 3** illustrates analytical parameters for these methods, and **Tables 1** and **2** list compositional data we obtained for glycoalkaloid levels in potatoes, potato leaves, and processed potato products. Detailed discussion of these methods is beyond the scope of this essay.

Analysis of freeze-dried samples offers the following advantages as compared to analysis of fresh samples (*74*, *87*): (a) it stops enzyme-catalyzed, wound-induced, and moisture-dependent compositional changes of glycoalkaloids; (b) it permits storage and transportation of samples for analysis; and (c) it makes it possible to relate composition to nutrition and safety; that is, the same samples can be used for both analysis of composition and incorporation into diets for feeding studies. A journal reviewer noted that during freeze-drying, water may not be removed quickly enough to inhibit enzymes prior to the application of heat to drive off residual moisture.

Glycoalkaloid Hydrolysis Products. The branched sugar side chains of the glycoalkaloids are susceptible to hydrolysis by either enzymatic action or acid catalysis. Generally, the glycoalkaloids are referred to as α compounds. Stepwise cleavage of the individual sugars of the glycoside leads to *β* and *γ* compounds in the case of trisaccharide side chains and *β*, *γ*, and *δ* compounds derived from the tetrasaccharide of tomatine (**Figure 2**).

For potato and tomato glycoalkaloids, acid hydrolysis rates generally increase with higher acid concentrations and temperatures and decrease with increasing proportions of water in mixed organic solvent−water solutions (*45*, *83*, *88*−*90*). The nature of the alcohol present in the aqueous−nonaqueous media strongly influenced the hydrolysis course. It is likely that the described conditions will produce similar results when applied to the other steroidal glycosides. It is not known whether structural features of the steroidal moiety influence hydrolysis, as is the case with the steroidal strophanthidin acetates (*91*).

ROLE IN THE PLANT

Biosynthesis. Glycoalkaloids are produced in all parts of the potato plant including leaves, roots, tubers, and sprouts. The biosynthesis proceeds via the cholesterol pathway via the following steps: acetate (C_2) → mevalonate (C_6) → isopentenyl pyrophosphate (C_5) → squalene (C_{30}) → cholesterol (C_{27}). Cholesterol generates the unsaturated aglycon solanidine and cholesteranol, the saturated demissidine. These biosynthetic events are discussed in detail elsewhere (*1*, *72*, *92*, *93*). The following are some specific observations: (a) The steroidal alkaloids occur in plants as glycosides. (b) Glycoalkaloids are both synthesized and are then degraded in the plant. (c) Glycoalkaloids occurring in roots and tubers are not transported upwardly. (d) Glycoalkaloid biosynthesis usually begins during germination and reaches a peak during the flowering period. Leaves attain a maximum glycoalkaloid concentration first, followed by an even higher concentration in unripe fruits and flowers. (e) The nature and concentrations of glycoalkaloids are genetically determined. (f) Total amounts are influenced by environmental factors such as soil and climate. (g) Postharvest exposure of potatoes to light and heat or mechanical injury stimulates glycoalkaloid synthesis.

To obtain additional information about the dynamics of these biosynthetic events, we examined the distribution of radioactivity among chlorophylls *a* and *b*, the individual glycoalkaloids α-chaconine and α-solanine, and other components of potato sprouts exposed to DL-mevalonate-2-^{14}C in the dark and in the light (*61*). Light-induced chlorophyll and glycoalkaloid formations appear to be independent biosynthetic events.

Glycosyltransferase enzymes catalyze the glycosylation of the solanidine aglycon to form the final glycosides. Cloning and antisense suppression of the gene encoding the enzyme that glucosylates solanidine to the monosaccharide *γ*-chaconine resulted in a decrease in glycoalkaloid content of transgenic potato plants harboring the suppressed gene (*56*−*59*, *94*−*98*). These findings may make it possible to create low-glycoalkaloid potatoes with improved compositional and nutritional qualities. See also below the section on Transgenic Potatoes.

Evolutionary Aspects of the Dual Glycoalkaloid Model. Although wild potato cultivars contain several structurally different glycoalkaloids, the evolution of commercial tubers seems to have dictated a convergence that resulted in the presence of only the two major potato glycoalkaloids, α-chaconine and α-solanine (*99*). During the evolutionary process, it is likely that nature initially created only one glycoalkaloid, probably α-solanine. As phytopathogens became adapted over time to resist its effects, the plant created by modifying the trisaccharide side chain a second, biologically more potent one, probably α-chaconine. Another possibility is that both glycoalkaloids were created concurrently to exert the observed synergistic effects described below. The second evolutionary approach allows the plant to have a smaller total amount of the two glycoalkaloids while maintaining resistance. Other possibilities are that one compound might be more effective against one set of pests and the other for a different set or that the availability (concentrations) of the different sugars required for the synthesis of the side chains dictated (was rate-determining for) the formation of two glycoalkaloids.

Inheritance of Glycoalkaloids. Glycoalkaloids can be passed to progenies during breeding programs designed to develop improved potatoes. Concentrations of commercially grown cultivars range from 1 to 35 mg/100 g of fresh weight and those of wild potatoes from 3.6 to 432 mg/100 g of fresh weight or up to 100 times more than those in cultivated varieties (*100*). In addition to α-chaconine and α-solanine, wild cultivars contain a number of other glycoalkaloids of largely unknown toxicity. Glycoalkaloid composition should be a major criterion for the release of new potato cultivars. Some recent studies are outlined here.

Relevant studies on inheritance showed that (a) the amount and type of glycoalkaloids varied among tubers of the parents and resistant hybrids created by somatic fusion of the cultivated potato *Solanum tuberosum* and the wild species *Solanum circaeifolium* (*101*); (b) potato tubers of somatic hybrids whose progenies were the cultivated potato *S. tuberosum* and the wild type *Solanum acaule* contained all four glycoalkaloids derived from the fusion parents **(Figure 4A)** (*60*); (c) interspecific somatic hybrids formed by protoplast fusion between *S. tuberosum and S. acaule* and between *S. tuberosum* and *Solanum brevidens* contained glycoalkaloids not detected in the parental species (*102*); (d) glycoalkaloids in genebank accessions of landraces of the cultivated potatoes contain only α-chaconine

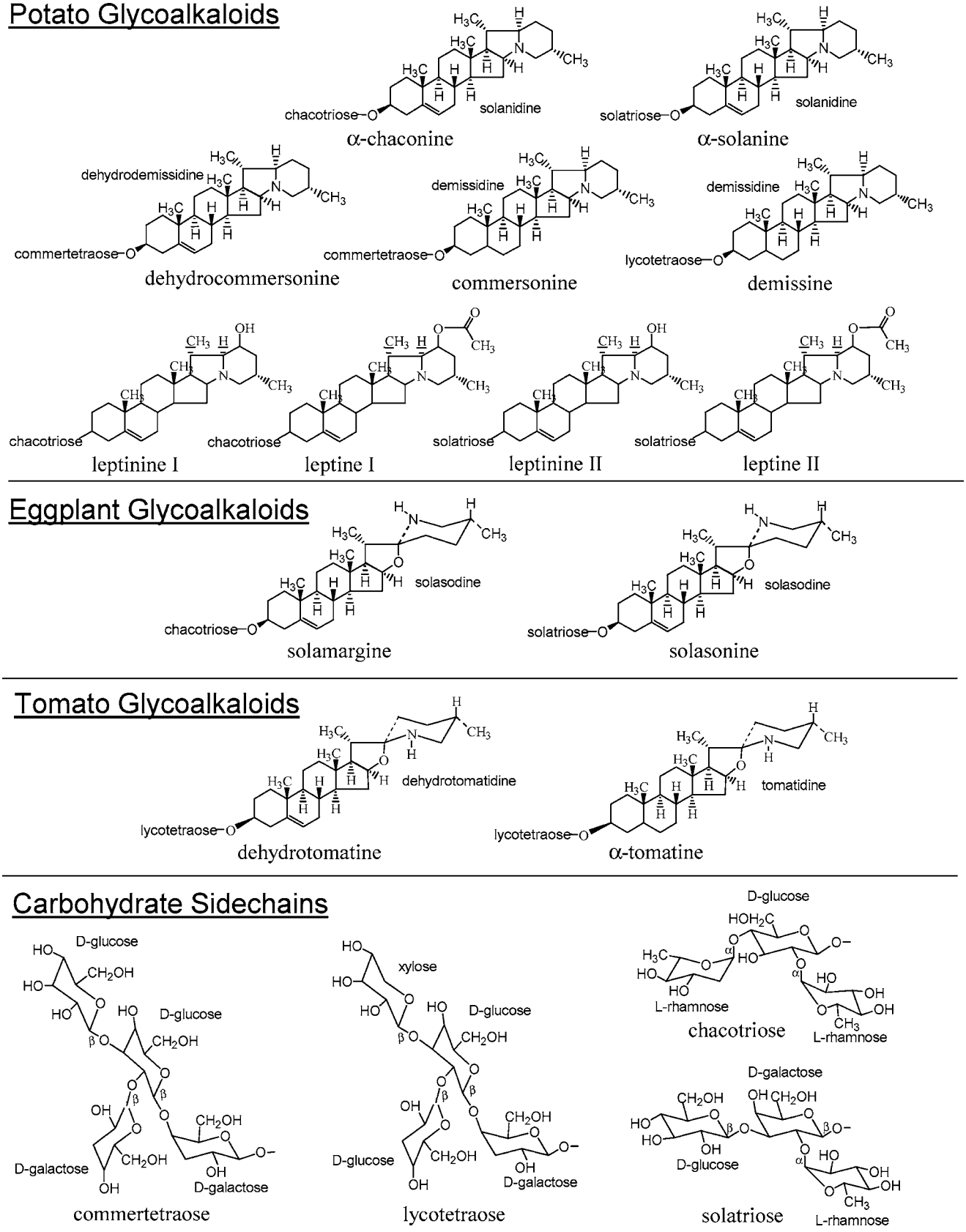

Figure 1. Structures of potato, tomato, and eggplant glycoalkaloids.

and α-solanine (*99*); and (e) three lines of *Solanum chacoense* are a potential source of genes governing the synthesis of foliar leptines (*103*). These results show that new cultivars can be created containing different types and levels of glycoalkaloids (*102, 104−107*).

Transgenic Potatoes. The creation of new transgenic potato cultivars with improved resistance against phytopathogens and improved composition is currently a very active area of worldwide research, as indicated by the following recent observations on glycoalkaloid-related aspects. The glycoalkaloid

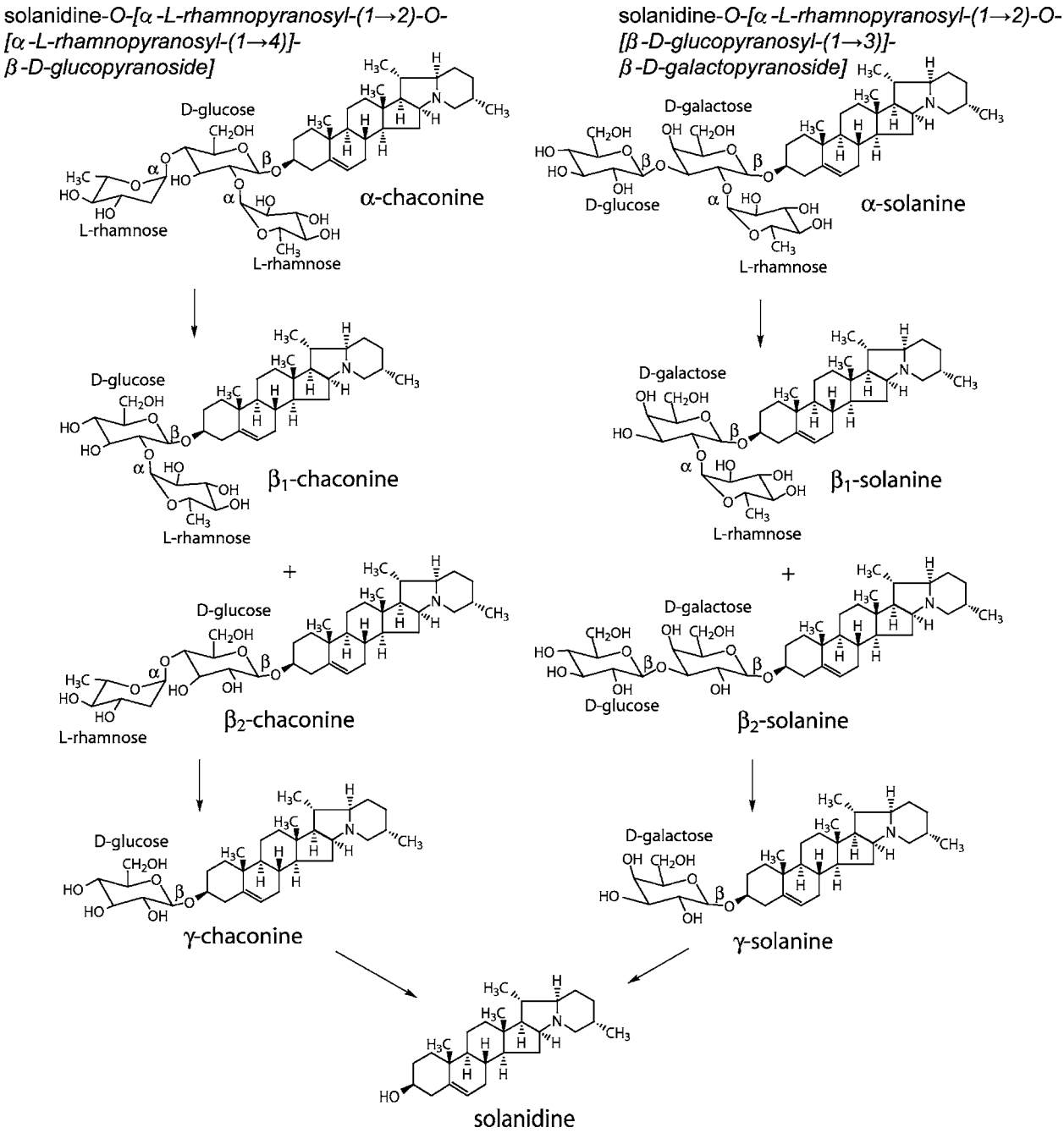

Figure 2. Intermediates in the hydrolysis of the trisaccharide side chains of α-chaconine and α-solanine to the aglycon solanidine.

content of the peel of a genetically modified cultivar, *S. tuberosum* L. cv. Desiree, was nearly double compared to those of control lines (*102*) (**Figure 4B**). However, overall, whole tubers produced by the virus-resistant clones were equivalent in glycoalkaloid levels to those of conventional varieties (*108*). The introduction of a potato virus Y gene does not seem to significantly alter content of glycoalkaloids (*109*). There was no significant difference between transgenic Spunta potatoes and the conventional variety in levels of glycoalkaloids, protease inhibitor, and phenolic compounds (*110a*). Analyses of the transgenic potato cultivars Record and Desiree by Shepherd et al. (*110b*) revealed a similar lack of differences from the normal varieties in the levels of glycoalkaloids, trypsin inhibitors, soluble carbohydrates, vitamin C, total nitrogen, and fatty acids. A rat feeding study revealed a slight difference in final body weights between the control and experimental groups, but no other differences in biochemical parameters and organ weights (*110a*).

Related studies have shown that (a) glycoalkaloid levels of improved transgenic potatoes were close to or lower than those of control cultivars (*65*); (b) repression of the ADP-ribosylation factor (ARF) in potato plants results in significant decreases in glycoalkaloid accumulation in the transgenic plants, with the level of α-chaconine about one-third of that observed in the normal plants (*111*); (c) the resistant (to potato virus × and to scab) potato variety had lower glycoalkaloid and reducing sugar levels and higher protein and vitamin C contents as compared to commercial tubers (*112*); (d) some overexpressed transgenic plants contained a 2-fold higher glycoalkaloid level and repressed plants a 2-fold lower level than did nontransgenic

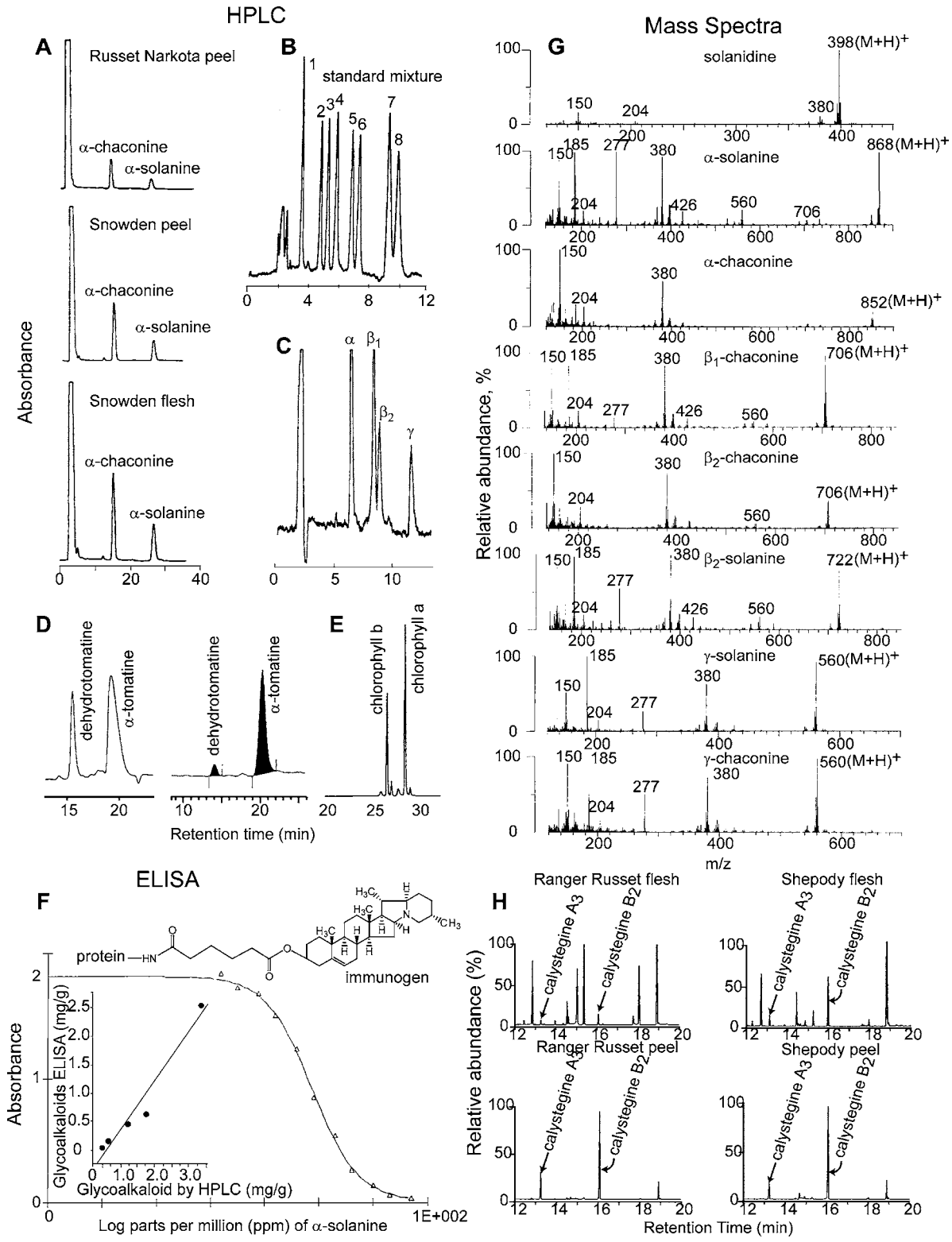

Figure 3. Analytical indicators: (**A**) HPLC of α-chaconine and α-solanine (*35*); (**B**) HPLC of potato hydrolysis products (standards) [1, solasonine; 2, α-solanine; 3, α-chaconine; 4, β_2-solanine; 5, β_1-solanine; 6, β_2-chaconine; 7, γ-solanine; 8, γ-chaconine (*32–35*)]; (**C**) HPLC of a partial acid hydrolysate of α-chaconine [α, α-chaconine; β_1, β_1-chaconine; γ, γ-chaconine (*32–35*)]; (**D**) HPLC of tomato glycoalkaloids dehydrotomatine and α-tomatine (*2*, *36–40*); (**E**) HPLC of chlorophylls *a* and *b* (*164*); (**F**) correlation between potato glycoalkaloid levels determined by ELISA and HPLC (*41–44*); (**G**) mass spectra of glycoalkaloids and hydrolysis products (*45*); (**H**) mass spectra of calystegines A_3 and B_2 isolated from potatoes (*35*).

tubers (*84*); (e) a metabolomics study indicates that glycoalkaloid levels of genetically modified and conventional potatoes appear to be substantially equivalent (*113*); (f) glycoalkaloid levels of transgenic potatoes exposed to infection or environmental stress conditions differed significantly from that of control potatoes (*114*); (g) α-solanine activated (induced) invertase activity in the *Ricinus communis* plant (*115*), suggesting that glycoalkaloids may influence sucrose hydrolysis in potato and other plants;

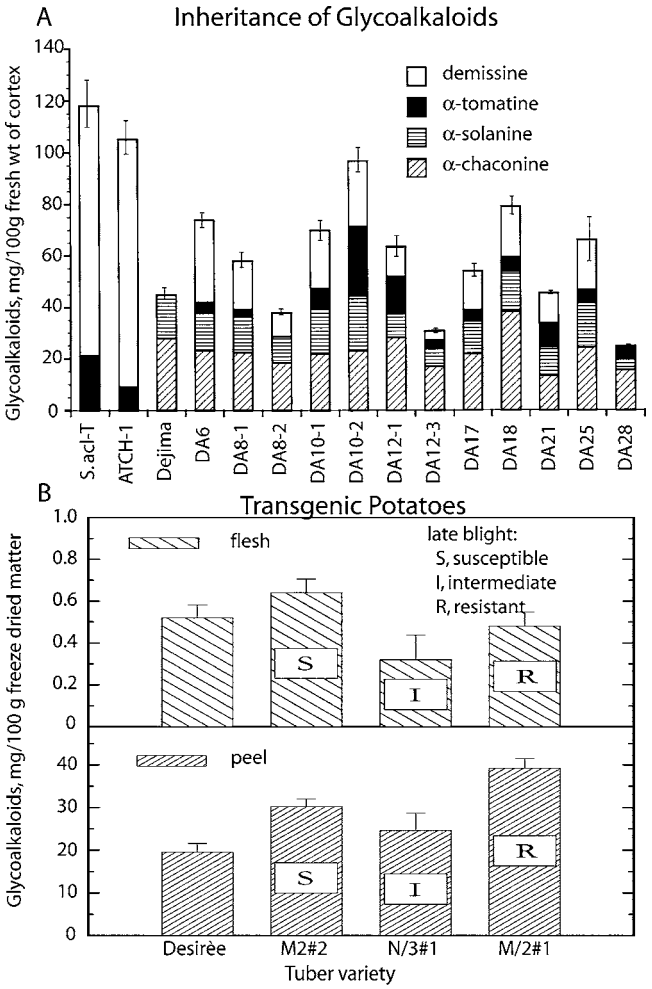

Figure 4. (**A**) Constitutent glycoalkaloids in the cortex of *S. acaule*-T, the fusion parents of *S. acaule* and *S. tuberosum*, and 12 somatic hybrids (*60*); (**B**) distribution of glycoalkaloids in blighted and blight-resistant transgenic potatoes (*102*).

and (h) potential medical applications of high-glycoalkaloid cultivars merit study (*116*). These and additional observations (*117*, *118*) indicate that genetic engineering involving suppression of gene expression governing the biosynthesis of cholesterol and/or the trisaccharide side chain of glycoalkaloids (and/or induced mutations) in these genes may decrease or increase both total amounts as well as ratios of α-chaconine and α-solanine in the transgenic potatoes.

Because glycoalkaloid and leptine levels of potato leaves may be involved in protecting the plant against phytopathogens, the levels of both tubers and leaves of transgenic plants should be compared to control plants. Do genetic manipulations of glycoalkaloids in tubers affect leptine levels of leaves and vice versa? Moreover, because the free amino acid asparagine and the reducing sugars glucose and fructose are the major precursors of potentially toxic acrylamide formed during frying and roasting of potatoes, compositional analysis of transgenic potatoes should include free amino acids and carbohydrates as well as the influence of storage on levels of free glucose (*119*).

Organically Grown Potatoes. Although glycoalkaloid levels varied widely from variety to variety, the pooled mean level for eight Czech varieties grown in controlled field studies was higher in organically grown tubers (80.8 ± 44.5 mg/kg) than in conventional ones (58.5 ± 44.1 mg/kg) (*66*). Although the overall difference is not statistically significant, three varieties grown organically (Rosara, Rosella, and Monalisa) had statistically significantly higher glycoalkaloids levels than the corresponding conventional ones. The organic tubers also contained higher chlorogenic acid (208 ± 114 mg/kg) levels compared to the conventional ones (159 ± 92 mg/kg) as well as higher vitamin C levels. Polyphenol oxidase activity and the rate of enzymatic browning were also higher in the organic potatoes. Because organically grown potatoes are not exposed to pesticides and herbicides, they seem to compensate by synthesizing higher levels of the natural resistant factors including glycoalkaloids and antioxidative phenolic compounds. It is not known whether the higher levels of glycoalkaloids, vitamin C, and chlorogenic acid in the organic potatoes will be reflected in improved nutrition and health, which are also governed by the carbohydrate, free amino acid, and protein contents of the tubers. These potato ingredients were not measured in this well-designed comprehensive study.

Resistance to Colorado Potato Beetles. Potato plants stressed by Colorado potato beetles (*Leptinotarsa decemlineata*) produced tubers with a higher glycoalkaloid concentration than unstressed plants (*82*). These results imply that potatoes from plants stressed by the beetles may not be as safe to consume as those protected by safe synthetic pesticides. Resistance to the beetles has been associated with foliar potato glycoalkaloids called leptines—acetylated forms of α-chaconine and α-solanine (**Figure 1**) (*120*−*123*). Neither the larvae nor the adults sequestered either α-chaconine or α-solanine from potato foliage (*124*). Higher levels of glycoalkaloids at the periphery of the tuber can impart strong resistance, provided the high content is compensated by low internal levels, which do not exceed recommended levels for human consumption. The significance of leptines for the human diet is not known.

Nematocidal Activity. A study of the structure−activity relationship of plant steroids showed that maximum phytoparasitic nematocidal activity against root-node nematodes was exhibited by glycosides such as α-chaconine and solamargine containing the chacotriose side chain (*125*).

Glycoalkaloid−*Phytophthora infestans* Relationships. Studies report variable results on possible relationships between glycoalkaloid levels of potato leaves and tubers and infection by *P. infestans*, a fungus responsible for major damage to potato crops. *P. infestans* induced glycoalkaloid accumulation in potato leaves grown in Russia (*126*), but not in potato clones grown in the United States (*127*). Other studies found that *P. infestans* affected glycoalkaloid production and induced production of phytoalexins, mainly rishitin and lubimin, in tubers and tuber disks (*128*−*132*). Infection of potato tubers by *P. infestans* induced increases in sesquiterpene cyclase and squalene synthase, enzymes of the isoprenoid pathways. These enzymes catalyze the synthesis of both sesquiterpenoid phytoalexins and glycoalkaloids (*133*). Tuber glycoalkaloids were not responsible for the resistance to late blight of hybrids (*134*). On balance, it appears that glycoalkaloid levels of blighted potatoes do not differ from normal ones.

Distribution of Glycoalkaloids in Whole Tubers. The majority of glycoalkaloids in the potato tuber are located within the first 1 mm from the outside surface and decrease toward the center of the tuber (*35*, *135*). Tubers of several cultivars showed an uneven distribution of α-chaconine and α-solanine, with the highest levels around the eyes of the outer layer (periderm, cortex, and outer phloem) (*136*, *137*). Peeling of the tissue 3−4 mm from the outside before cooking removes nearly all of the glycoalkaloids. Both rates and patterns of accumulation as well as α-chaconine to α-solanine ratios during tuber growth and development are strongly influenced by genotype (*138*).

Total levels generally decrease with increasing tuber size. Cultivars such as Rocket that showed a low rate of accumulation in relation to increasing tuber size and early cessation of accumulation are especially desirable as early-maturing potatoes that are harvested when the tubers are small and may be consumed unpeeled. The most pronounced increases in glycoalkaloid levels during storage occurred in the outer tuber layers. There appears to be variability among cultivars in their susceptibilities to light-induced glycoalkaloid synthesis (*139*).

Ratios of α-Chaconine to α-Solanine. The ratios of α-chaconine to α-solanine for selected potato samples ranged from 0.82 to 2.62 (**Tables 1** and **2**). The ratio for peel, generally in the range of about 2, was much higher than that for flesh with values near about 1.5. Because, as mentioned below, α-chaconine is more toxic than is α-solanine, it is desirable to have this ratio as low as possible. We can only speculate about possible reasons for the wide variations in these ratios. Because the two glycoalkaloids, which share the common aglycon solanidine but not the same trisaccharide side chain (**Figure 1**), appear to be synthesized via distinctly different (discrete) biosynthetic channels (*140*), it is possible that the rates of biosynthesis of the two glycoalkaloids in the different channels are cultivar-dependent. Another possible rationalization for the varying ratios is that the rate of metabolism of the two glycoalkaloids is also cultivar-dependent. These considerations imply that alteration of the genes encoding enzymes involved in the biosynthesis of α-chaconine and/or α-solanine may be mutually dependent.

None of the listed wet whole potatoes exceeded 200 mg of total glycoalkaloids/kg of potatoes. However, this was not the case for potato peel. The values for three wet peel samples (Atlantic, Dark Red Norland, and Russet Norkota) are <200 mg/kg and those for the other five, >200 mg/kg. High levels of glycoalkaloids in potato skins may be a concern for commercial products that have high skin/flesh ratios, for example, potatoes from which the flesh has been mostly removed and the skin is used to scoop up condiments such as salsa. Peel from potato-processing plant wastes may also be a concern if the peel is not thoroughly mixed with other waste streams.

Glycoalkaloids in Potato Leaves. Analysis of the foliar content of 645 accessions of 70 *Solanum* species and 6 hybrids revealed an average level of foliar glycoalkaloids of commercial potato cultivars of ~50 mg/100 g (*141*). Most of the *Solanum* species in the potato germplasm collection are low-foliar-glycoalkaloid species. Our analyses showed that fresh leaves contained 2235 mg/kg total glycoalkaloids and dehydrated (dry) leaves, 9082 mg/kg (*33*, *74*, *142*).

Variability in the analysis of leaf glycoalkaloids was minimized by comparing single leaves from the same stem position of each plant (*74*, *87*). Comparisons involving other leaves indicated that the glycoalkaloid content was not constant with respect to either time or position on the stem. Determining glycoalkaloid levels on a dry rather than fresh weight basis reduced variability. The method of drying the samples had no influence on the variability of data. In breedings involving repeated planting and analyses, plants of one or more control varieties should always be grown.

Leptines in Potato Leaves. Another group of closely related glycoalkaloids called leptines are present in the leaves of a special accession of *S. chacoense* Bitt (*143*). The leptines are soluble at high pH—the most common method of precipitating glycoalkaloids for analysis—and are lost in many analytical methods. Leptines impart resistance to the potato beetle (*144*).

Enzymatic Hydrolysis of Glycoalkaloids in Tubers. Sprouts, tubers, and blossoms contain hydrolytic enzymes that cleave individual sugars from α-solanine and α-chaconine (*145*−*147*). These enzymes may be part of the metabolic apparatus involved in metabolism via degradation of glycoalkaloids in the plant in order to avoid autotoxicity. Moreover, although certain fungi seem to contain hydrolytic enzymes presumably to protect themselves against the antibiotic action of glycoalkaloids (*148*, *149*), it is not known whether glycosidases present in the gut of mammals have any effect on glycoalkaloids.

OTHER SECONDARY METABOLITES IN POTATO TUBERS

In addition to glycoalkaloids, potato plants synthesize several other biologically active compounds. These have the potential of affecting both adverse and beneficial effects of the glycoalkaloids in the plant and in the diet. The following compounds fall into this category: (a) calystegine alkaloids, having structures resembling those of atropine (*35*, *150*, *151*) and dietary significance meriting study; (b) antioxidative phenolic compounds such as chlorogenic acid, the content of which as well as that of glycoalkaloids increases during greening of potatoes (*33*, *142*, *152*, *153*) and which participate in enzymatic browning reactions that can be inhibited by SH-containing amino acids and peptides (*154*−*157*); (c) protease inhibitors of digestive enzymes (*142*) analogous to those present in soybeans (*158*, *159*) and which may be of value in the treatment of peri-anal dermatitis in humans (*160*); (d) lectins (*161*), glycoproteins that inhibit the growth of human breast cancer cells (*162*); (e) chlorophylls (*33*, *61*, *163*, *164*), considered to be possible dietary anticarcinogens (*165*); and (f) phytoalexins, secondary metabolites induced by parasitic fungi such as *P. infestans* (*166*), which may contribute to adverse effects of glycoalkaloids in blighted potatoes (*28*).

POSTHARVEST EFFECTS ON GLYCOALKOLOIDS

Effects of Processing and Storage. Glycoalkaloid levels can vary greatly in different potato cultivars and may be influenced postharvest by environmental factors such as light (*142*, *167*−*169*), mechanical injury (*170*, *171*), and storage (*172*−*174*). For example, the increase in glycoalkaloid content of Czech potato varieties exposed to light for 14 days (68.6 mg/kg) was double that observed after a 7-day exposure (33.1 mg/kg) (*168*, *175*).

Home processing methods (boiling, cooking, frying, and microwaving) have small and variable effects on glycoalkaloids (*176*, *177*). For example, boiling potatoes reduced the α-chaconine and α-solanine levels by 3.5 and 1.2%, respectively; the corresponding loss during microwaving was 15% (*177*). Whereas there was no change during deep-frying at 150 °C, at 210 °C, the loss after 10 min was ~40%. Significant degradation starts at ~170 °C.

Potato Fries, Chips, and Flakes. Chips and potato peel products from different grocery stores and restaurants contained significant but variable amounts of glycoalkaloids (**Table 2**) (*32*, *178*, *179*). Glycoalkaloids are stable during cooking in frying oil at 180 °C (*180*). However, a continuous diffusion of glycoalkaloids into the oil occurred as subsequent batches of potatoes with peels were cooked in the same oil (**Figure 5A**). As the oil becomes saturated with glycoalkaloids, diffusion may occur from the oil back into the potato matrix. Because of a lack of guidelines for changing the oil, this observation may explain the wide variation in glycoalkaloid content of commercial French fries obtained from different restaurants.

Peksa et al. (*181*) observed 72−76% decreases in glycoalkaloid levels, but not in the 2.5:1 ratio of α-chaconine to

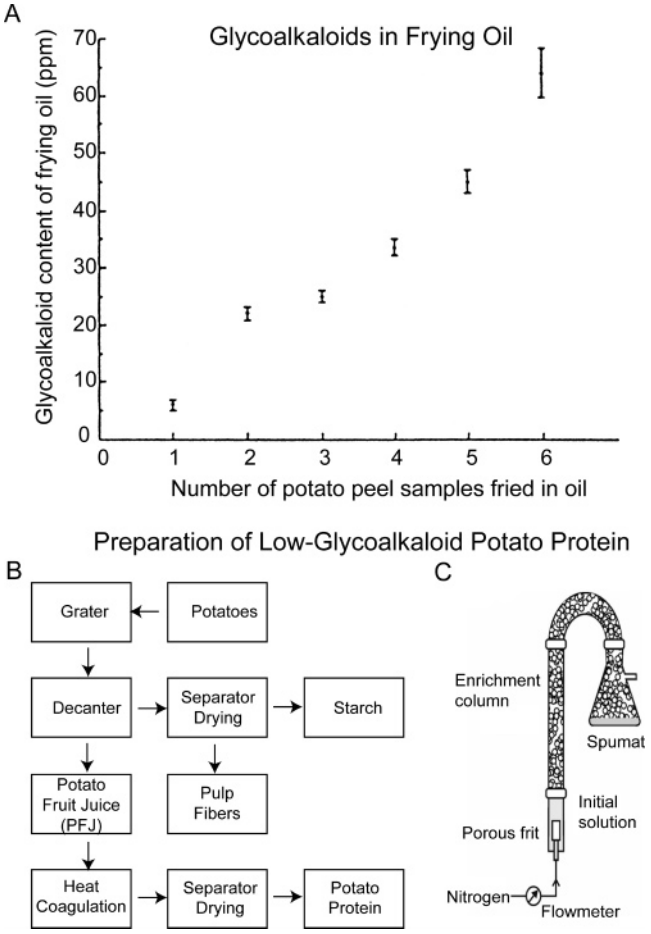

Figure 5. (**A**) Increases in glycoalkaloid levels of frying oil during consecutive fryings of potato peel in the same oil (*180*); (**B**) flowchart for the isolation of potato protein (*63*); (**C**) adsorptive bubble apparatus for the separation of glycoalkaloids from potato juice (*64*). Separation of the glycoalkaloids takes place on a glass column packed with a foam with nitrogen as the carrier gas.

α-solanine, during the process of chip production. Peeling, slicing, washing, and frying contributed to the observed decrease during the preparation of the chips. Most of the glycoalkaloids were removed during peeling, blanching, and frying (*182*). Glycoalkaloid levels of both fries and chips can be minimized by using peeled, sliced, and washed potatoes and by frequent changes of frying oils. The presence of sulfur compounds reduced both protease inhibitor and glycoalkaloid content during extrusion cooking of potato flakes (*183*). Thus, the glycoalkaloid level of flakes treated with 1% DL-methionine−HCl was 0.71 mg/100 g compared to 1.77 mg/100 g for the untreated control.

Potato Peel. Potato peel constitutes a rich source of glycoalkaloids and phenolic antioxidants. Peel has the potential to ameliorate diabetes (*184*) as well as being a source of dietary fiber. Fried and baked potato skins are popular appetizers in restaurants. **Table 2** shows that the glycoalkaloid content of four skins we obtained from four restaurants ranged from 56.3 to 203.0 mg/kg of original product. Subjecting potato peel derived from French fry production to extrusion at 110 or 150 °C did not change glycoalkaloid levels (*185*). There was no decrease in the original α-chaconine or α-solanine levels (39 and 80 mg/100 g, dry weight basis, respectively).

Low-Glycoalkaloid Potato Protein. Our studies (unpublished results) revealed that a commercial potato protein concentrate contains significant amounts of glycoalkaloids (~200 mg/100 g). If potato protein isolates are to assume a greater role in animal and human nutrition, a need exists to reduce their glycoalkaloid content. Efforts to minimize the glycoalkaloid content appear to have succeeded, as indicated by the following observations. Potato fruit juice prepared from potato tubers contains about 20 g of protein/L (*63*) (**Figure 5B**). To minimize the presence of glycoalkaloids that may be coextracted into the juice, Backleh et al. (*64*) devised an adsorptive bubble separation method with a pH gradient, which can remove nearly all of the glycoalkaloids from the juice (**Figure 5C**).

Although potatoes contain only about 2% protein on a fresh basis (*186*), the value increases to about 10% when examined on a dry basis, a value that is equal to that of cereals such as rice or wheat (*187*). Furthermore, because the potato protein has higher levels of the essential amino acid lysine, it is of higher nutritional quality than that of wheat protein, which has insufficient amounts of two essential amino acids: lysine, the first nutritionally limiting, and threonine, the second limiting one (*187*). Feeding studies showed that the potato concentrate's nutritional quality was found to be excellent (*188*, *189*). Kerr et al. (*190*) observed lowered food intake, growth, and differences in performance of pigs fed a high-glycoalkaloid potato protein (303.0 mg/100 g). By contrast, a low-glycoalkaloid (15.6 mg/100 g) protein diet was equivalent in quality to a fish protein diet. These observations are similar to our own studies on the feeding of rats (*191*). Feeding dietary high-glycoalkaloid potato protein to salmon resulted in severe weight loss, whereas a low-glycoalkaloid potato protein was highly nutritious without apparent adverse effects (*192*). Human feeding trials also indicate that potato proteins are of a very high quality, possibly higher than calculated from the amino acid composition (*193*). These observations show the potential value of low-glycoalkaloid potato proteins in animal and human nutrition.

The fungus *Cephalosprorium eichhorniae* (ATCC 38255) was used to convert potato-processing wastes into microbial protein for use as animal feed (*194*). The growth of this fungus was not inhibited by α-solanine or β-chaconine.

ENZYME AND HORMONAL ASPECTS

Inhibition of Cholinesterases. Glycoalkaloids (as are most pesticides) are inhibitors of the enzymes acetylcholinesterase (EC 3.1.1.7, AChE) and butyrylcholinesterase (EC 3.1.1.8, BuChE). Both enzymes catalyze the hydrolysis of the neurotransmitter acetylcholine at the synapse in the central nervous system, as illustrated with the acetylcholinesterase enzyme (*195*):

$$\underset{\text{acetylcholine}}{(CH_3)_3N^+CH_2CH_2OCOCH_3} + \underset{\text{acetylcholinesterase}}{\text{Enz-O-OCCH}_3} + H_2O \rightarrow \underset{\text{choline}}{(CH_3)_3N^+CH_2CH_2OH} + \underset{\text{acetate}}{HOCOCH_3}$$

Pokrovskii (*15*) seems to have been one of the first to report that water extracts of sprouting potato tubers and the glycoalkaloids solanine and tomatine inhibited the activity of blood serum AChE and less so brain AChE. Later studies revealed that α-solanine and α-chaconine were strong inhibitors of both AChE and BuChE (*16*, *62*, *196*−*203*).

α-Solanine and α-chaconine are about equal in potency with regard to in vitro inhibition of bovine and human AChE (*200*) (**Figure 6A**,**B**). Mixtures of chaconine and solanine were found to be slightly antagonistic. β_2-Chaconine was as effective as α-chaconine. The corresponding aglycons solanidine, tomati-

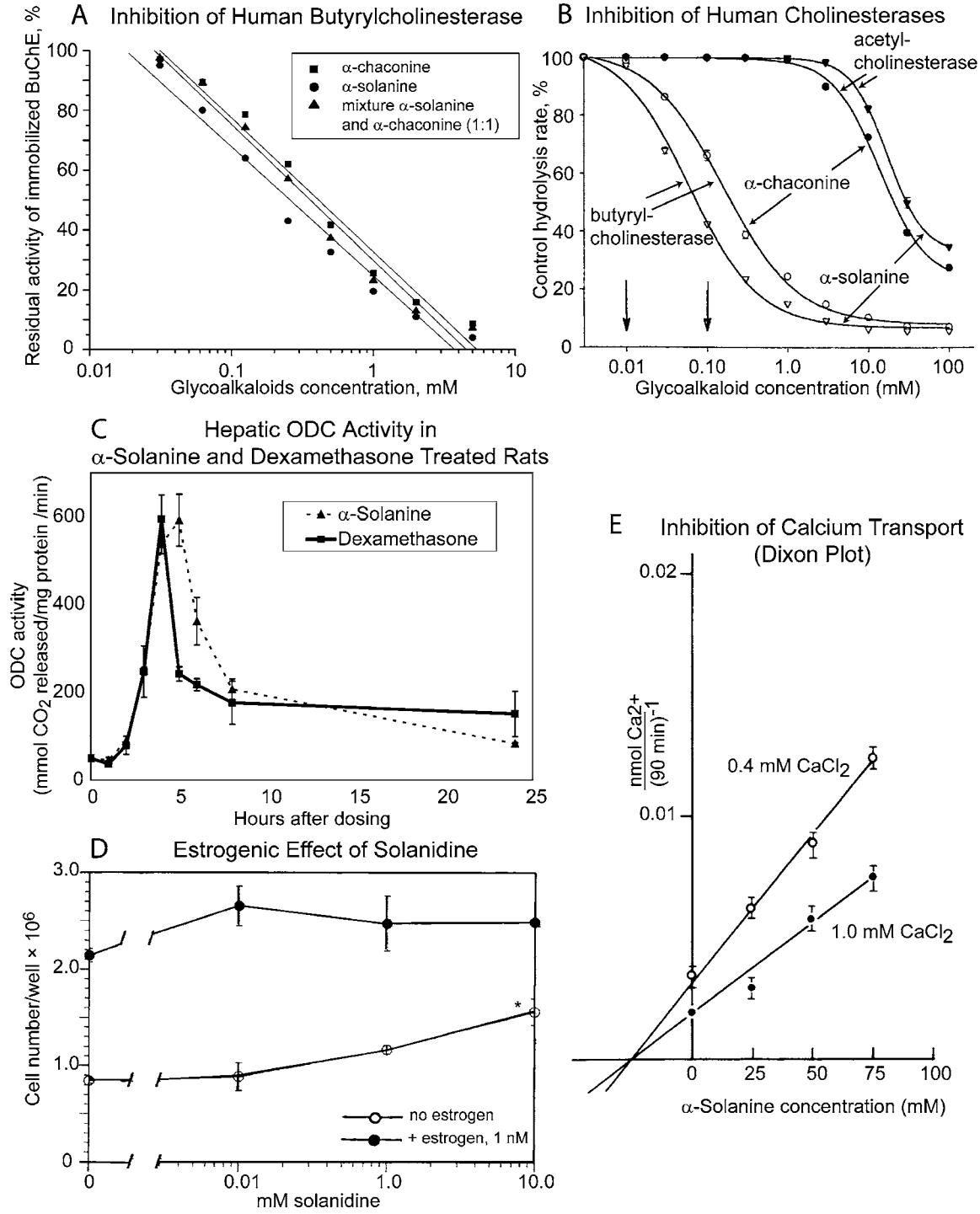

Figure 6. Enzyme and hormonal effects of glycoalkaloids: (**A**, **B**) dose dependence of the inhibition of cholinesterases (*62*, *204*); (**C**) time course of the in vivo induction of ornithine decarboxylase in rat livers (*207*); (**D**) estrogenic activity of solanidine in cell assays (*209*); (**E**) inhibition of calcium transport in the rat intestine by α-solanine (*210*).

dine, and solasodine had little or no inhibitory effects. In contrast to its cell disruption activity, the structure of the steroid appears to be more important than that of the sugar side chain in determining AChE inhibition. However, the presence of a sugar side chain is obligatory for AChE inhibition to occur. The following relative potencies of α-chaconine inhibit insect acetylcholinesterases (IC_{50} in μM): German cockroach, 8.7; mosquito, 9.4; housefly, 35.2; cottonwood leaf beetle, >40; Colorado potato beetle, 863 (*201*). Because a lower IC_{50} value indicates greater inhibitory activity, the potato beetle enzyme was the least susceptible to inhibition. The high resistance of the potato beetle enzyme to inactivation may be the result of an adaptation to long-term consumption by beetles of potato leaf glycoalkaloids. Glycoalkaloids behaved differently toward cholinesterases than did organophosphorus and carbamate insecticides (*201*, *203*). The differences may be due to differences in respective binding affinities to the esteratic and/or serine active sites of the enzyme.

α-Chaconine and α-solanine are reversible inhibitors of human plasma BuChE (*203*). Harris and Whittaker (*197*) found that different human populations have different susceptibilities to AChE inhibition, dividing people into three types: usual,

intermediate, and atypical. Glycoalkaloids extracted from potato sprouts inhibited 63% of human serum cholinesterase, compared to 52% for α-solanine, 41% for α-chaconine, and 0% for solanidine (*202*).

Co-administration of potato glycoalkaloids (30−100 nM) with mivacurium (a neuromuscular blocking drug used as a general anesthetic that inhibits cholinesterases) to rabbits resulted in additive inhibition (*204*). Glycoalkaloids also prolonged the recovery time from mivacurium-induced muscular paralysis by ∼50%. The observed wide variation in recovery time from anesthesia may be the result of consumption of potato-containing diets prior to anesthesia. As part of this study, the author determined the following cholinesterase IC_{50} values (in μM): AChE, 17 (α-chaconine), 14 (α-solanine); BuChE, 0.066 (α-chaconine), 0.17 (α-solanine).

Symptoms indicative of central nervous system damage attributed to the ability of glycoalkaloids to inhibit AChE include rapid and weak pulse, rapid and shallow breathing, delirium, and coma. The mechanism of inhibition by glycoalkaloids probably involves non-covalent competitive binding to the active site of the enzyme. Additional structure−inhibitory activity relationships showed that (a) the unshared electron pair on the ring nitrogen of the aglycon may be required for formation of bioactive iminium ions (*205*) and (b) the nitrogen-containing E/F ring of the aglycon is a more important determinant of anticholinesterase activity than is the carbohydrate side chain. This is confirmed by observations of similar activities of α-chaconine and α-solanine, both of which share the same aglycon but contain different side chains (*24*).

Induction of Ornithine Decarboxylase in Rat Livers. Ornithine decarboxylase (ODC) catalyzes the decarboxylation of ornithine to putrescine as shown below.

$$\underset{\text{ornithine}}{H_2N(CH_2)_3CH(NH_3^+)COO^-} + ODC \rightarrow \underset{\text{putrescine}}{H_2N(CH_2)_4NH_2} + CO_2$$

Putrecine is the foundation molecule of the polyamines, which are highly cationic molecules that interact with DNA. Induction of ODC indicates that the enzyme is involved in the regulation of cell division (*206*). Our studies (*207*) showed that the intraperitoneal administration of α-chaconine, α-solanine, and solanidine at 7.5, 15, and 30 mg/kg of body weight produced markedly elevated induction of ODC activity in rat livers at 4 h post-treatment, with a linear dose response (**Figure 6C**). The following relative effects in terms of specific activities were noted at 17 mM/kg of body weight: control, 49.6; solanidine, 93.0; α-solanine, 359.2; α-chaconine, 561.8. ODC activity with dexamethasone, a glucocorticoid hormone, followed a pattern similar to that of α-solanine. The nature of the carbohydrate side chain dictates induction of ODC, a marker of liver cell proliferation. It is not known whether orally administered glycoalkaloids would induce ODC in humans.

Estrogenic Effects of Solanidine. Because we had previously found that oral consumption by mice of the aglycons and the natural steroid dehydroepianoandrosterone (DHEA) induced an increase in liver weights of mice and, also, in view of structural similarities among the aglycons, DHEA, and estrogenic hormones such as estradiol, it was of interest to find out whether the aglycons possess estrogenic activity (*208*). Solanidine, but not the parent glycoalkaloids α-chaconine and α-solanine, exhibited low estrogenic effects in vitro (*209*) (**Figure 6D**). The dietary significance of the apparent estrogenic effect of solanidine remains to be ascertained.

CELL MEMBRANE STUDIES

Glycoalkaloids have been shown to interfere with transport across cell membranes of Ca^{2+} (*210*, *211*) and Na^+ (*49*, *51*) ions. Thus, Michalska et al. (*210*) found that 5 mM solanine solutions (pH 6.4) inhibited active calcium transport in the rat duodenum when administered in drinking water for 12 days and when added to their inverted intestine sacs in vitro. **Figure 6E** shows the noncompetitive inhibition by solanine, with an inhibitory constant of 0.25 μM.

Potato, tomato, and eggplant glycoalkaloids alter the membrane potential of *Xenopus laevis* frog embryos (*49*−*51*, *53*, *212*−*215*). They also influence the active transport of sodium by adult frog skin. These results suggest that one possible mechanism of action of glycoalkaloids may involve direct or indirect effects on active transport across cell membranes. One approach to gauge the membrane potential is to use a fluorescent probe, usually termed an electrochromic dye. Fluorescence of the dye is altered directly in response to changes in membrane potential (**Figure 7A**).

Because relative potencies of glycoalkaloids were found to be similar for frog embryo effects (survival and teratogenicities) and for membrane effects (membrane potential), alteration in ion channels could explain glycoalkaloid toxicity, including teratogenicity. Studies are needed to find out whether systemic effects of glycoalkaloids in primates would mirror those observed in vitro.

Another clue to the mechanism by which the test compounds act is afforded by the observed effects on frog skin interstitial short-circuit current (ISC) in an Ussing chamber (*51*). ISC, a measure of transepithelial active transport of sodium, decreased up to 30% at an α-chaconine concentration of 10 mg/L (**Figure 7B**). α-Solanine had a similar but smaller effect, decreasing ISC by 16%. Solanidine was inactive. These results suggest that one way by which glycoalkaloids exert biological effects is to modify active transport of sodium and that frog skin is a useful experimental model to evaluate effects of glycoalkaloids at the cellular level.

The same cell membrane-disrupting mechanism also appears to operate with plant pathogenic fungi such as *P. infestans* (*214*, *215*). The extent of cell disruption measured by a fluorescence assay correlated with the extent of growth inhibition of the fungi. This assay should permit rapid evaluation of the effectiveness of other fungicides.

Glycoalkaloid−Cholesterol Relationships. One possible mechanism for both toxic and anticarcinogenic action of the glycoalkaloids is disruption of cholesterol-containing cell membranes. α-Chaconine and α-tomatine formed strong complexes with cholesterol and other phytosterols in vitro (*216*) (**Figure 8E**). It has been postulated that at least part of the glycoalkaloids' ability to disrupt membranes is due to sterol binding (*217*, *218*). Glycoalkaloids interacted with sterol-containing membranes, resulting in membrane disruption in the following potency order: α-tomatine > α-chaconine > α-solanine (*25*−*27*). The proposed mode of action involves insertion of the aglycon part in the membrane bilayer and complex formation with membrane sterols, followed by rearrangement and disruption of the membrane structure and leakage of the cell content. α-Chaconine and solamargine, both with a chacotriose side chain, have been shown to have potent lytic action, whereas α-solanine and solasonine, both having a solatriose side chain, and β_2-chaconine, lacking one rham-

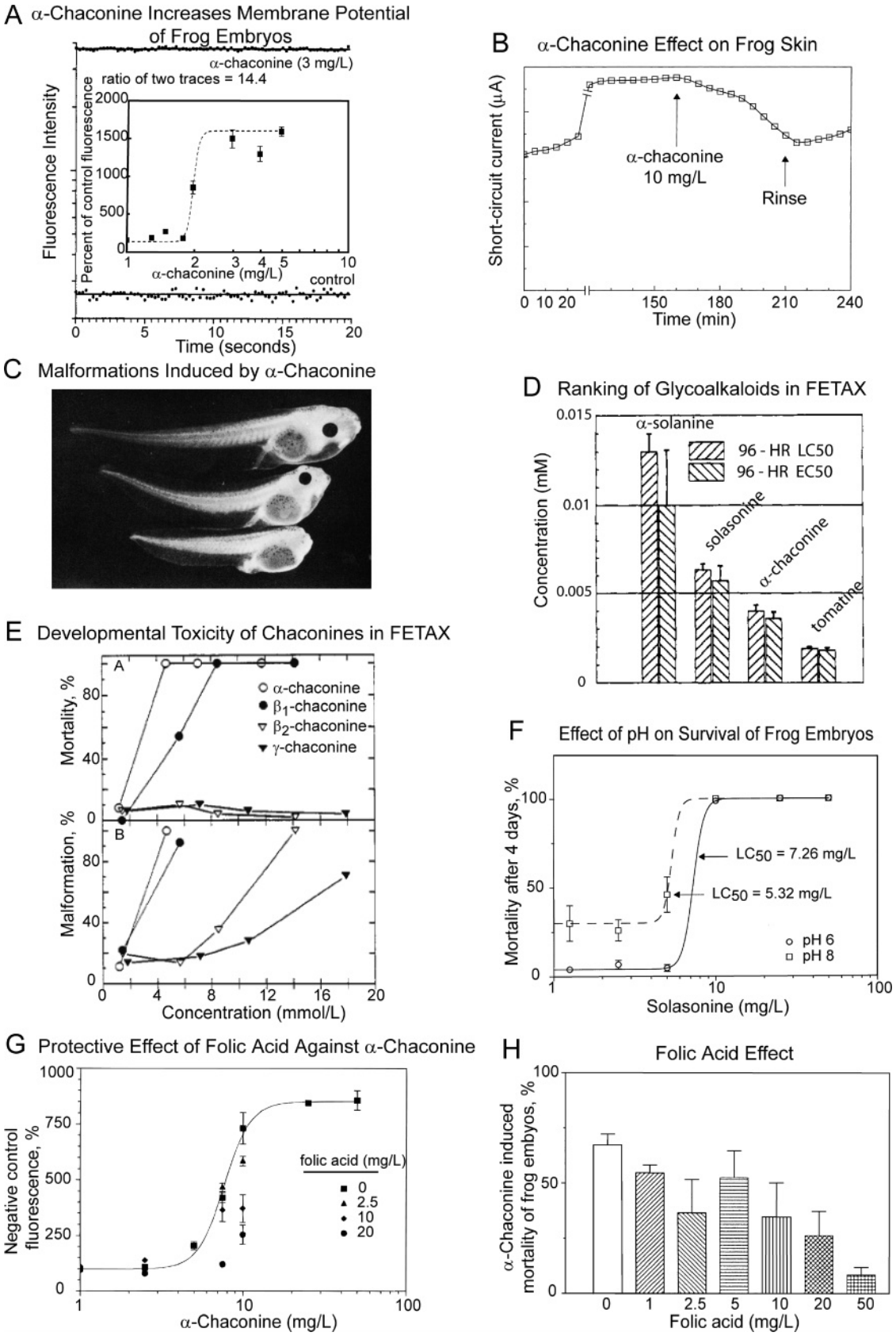

Figure 7. Malformations and cell membrane effects induced by α-chaconine in frog embryos and frog skin: (**A**) effects of α-chaconine on the membrane potential of frog embryos (*49*); (**B**) α-chaconine-induced short-circuit current in frog skin (*51*); (**C**) increase in α-chaconine concentration causes a progressive decrease in embryo length and developmental delay compared to the control (top embryo) (*46*); (**D**) ranking of four glycoalkaloids based on relative 96-h LC_{50} and EC_{50} values [concentration causing 50% mortality and malformations, respectively (*47*); the lower the value, the higher the developmental toxicity]; (**E**) developmental toxicities of α-chaconine hydrolysis products (*48*) (toxicity generally decreases on removal of carbohydrate groups from the trisaccharide side chain of α-chaconine); (**F**) α-chaconine causes higher mortality of frog embryos at pH 6 than at pH 8 (*50*); (**G**, **H**) protective effects of folic acid against α-chaconine-induced disruption of embryo cell membranes and malformations (*52*, *53*).

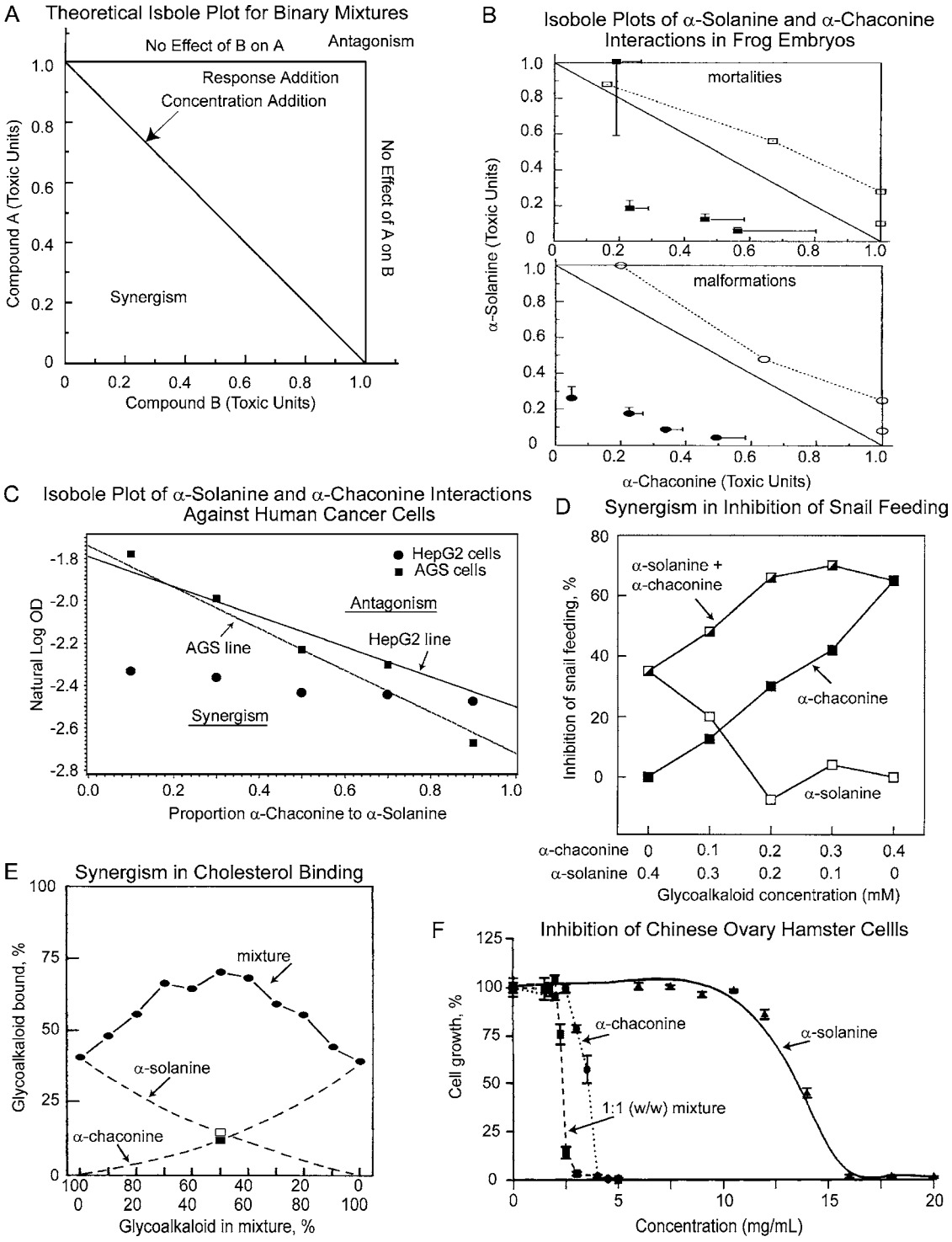

Figure 8. Synergistic effects of binary mixtures: (**A**) isobole plot for determining binary interactions (*55*); (**B**) frog embryo teratogenicity assay—*Xenopus* (FETAX) of mortalities and malformations of frog embryos (*55*); (**C**) activities against human cancer cells (*68*, *69*); (**D**) inhibition of snail feeding (*232*); (**E**) enhancement of cholesterol binding (*230*); (**F**) inhibition of growth of Chinese ovary hamster cells (*231*).

nose unit, have little effect in cell-disruption. Why membrane disruption is prevented by slight differences in the sugars of the triose, or the loss of one rhamnose from the lysis-active chacotriose, has yet to be explained. Obviously, the nature of the hydrophilic sugar moiety has much more influence than the structure of the steroid. Plausible rationalizations of the molecular mechanisms that may govern cholesterol−alkaloid/glycoalkaloid−cell membrane relationships in larvae of red flour beetles and tobacco hornworms are discussed in ref *219*.

This cell-disruption effect may also at least be minimally responsible for the observed organ damage. Although glycoalkaloids seem to concentrate mostly in the liver, high concentration have also been found in other major organs of the body including kidney, heart, lungs, and brain. They cause various levels of organ damage (*220*−*227*) discussed below.

Tomatine-containing diets reduced the absorption and plasma levels of cholesterol and triglycerides in hamsters fed a high-cholesterol, high-fat diet (*228*, *229*). Tomatine appears to form complexes in the digestive tract with dietary and liver-generated

cholesterol. The insoluble complexes are then excreted into the feces. It is not known whether orally consumed potato glycoalkaloids also reduce dietary and liver-generated cholesterol by similar mechanisms.

FROG EMBRYO STUDIES

We determined the effects of glycoalkaloids and aglycons in the frog embryo teratogenesis assay—*Xenopus* (FETAX) in terms of the following parameters: median lethal concentration (LC_{50}) after 96 h of exposure; the concentration inducing gross terata in 50% of the surviving frog embryos after 96 h (EC_{50}, malformation); and the minimum concentration needed to inhibit growth of the embryos (*46*−*48*, *54*, *55*). α-Chaconine was teratogenic and more embryotoxic than was α-solanine (**Figure 7C**−**E**). The aglycons demissidine, solanidine, and solasodine were less toxic than the glycosides. Because the glycosides differ only in the nature of the trisaccharide side chain attached, the side chain must strongly influence embryotoxicity.

Figure 7F shows that following exposure to solasonine more embryos survived at pH 6 (LC_{50} = 5.32 mg/L) than did at pH 8 (LC_{50} = 7.26 mg/L). This result suggests that the ionized form of the solasonine nitrogen is probably involved in binding to receptor sites of frog embryo cells.

The developmental toxicity generally decreased with stepwise removal of sugar units from the chacotriose and solatriose side chains (**Figure 7E**). Note, however, that the activity of the diglycoside β_1-chaconine was nearly as great as that of α-chaconine, whereas the diglycoside β_2-chaconine exhibited low activity. Certain combinations of glycoalkaloids can act synergistically in the frog embryos and other cells (**Figure 8**) (*55*, *69*, *230*−*232*).

The extraordinary effects of α-chaconine merit further comment. This glycoalkaloid induced severe anencephaly in the brains of the embryos and less severe malformations in other organs. Many of the embryos were headless and died on day 3 of the test. At concentrations >3 mg/L, α-chaconine caused miscoiling of the gut, muscular and skeletal kinking, and slight craniofacial malformations. At concentrations of 4−5 mg/L, severe muscular kinking, craniofacial malformations, microencephaly, and anencephaly occurred. The adverse effects induced by α-chaconine were apparent at one-third the level required for α-solanine.

Protective Effects of Folic Acid. Spina bifida (the defective closure of the vertebral column) is one of the most serious neural tube defects compatible with prolonged life. Its incidence seems to be partly environmentally related and is much higher (up to 7−8 per 1000 births) in some parts of the world than others (*233*, *234*).

Folic acid is reported to both prevent and reduce the severity of neural tube defects in humans (*233*). For example, data on 4468 cases of spina bifida and 2625 cases of anencephaly in the United States revealed that that these birth defects show decreasing trends for white and Hispanic births but apparently not for black births (*234*). Our own studies revealed that folic acid also protected frog embryos against α-chaconine-induced disruption of cell membranes, lethality, and malformations (**Figure 7G**,**H**) (*52*). Because there appears to be a causal relationship between folate levels and glycoalkaloid toxicity, we extended our studies to two additional pterin derivatives, that is, methotrexate and L-monapterin (*53*). Methotrexate decreased α-chaconine-induced polarization, as did folic acid. In contrast, L-monapterin did not.

Protective Effects of Glucose-6-phosphate and Nicotine Adenine Dinucleotpide Phosphate. We observed that a metabolic activation system (MAS) (composed of Aroclor 1254-induced rat liver microsomes) led to a reduction of developmental toxicity in the FETAX assay (*54*). The protective effects of the MAS were not due to detoxification by microsomal enzyme systems, but rather to NADP and glucose-6-phosphate. Glucose-6-phosphate could possibly exert its protective effect by competing with the carbohydrate groups of α-chaconine for receptor sites on cell membranes in the frog embryos. The protective effects of glucose-6-phosphate have also been confirmed in other cells (*235*). Folic acid, glucose-6-phosphate, and NADP have the potential to ameliorate adverse effects of potato glycoalkaloids. Will they do so in vivo?

ANIMAL STUDIES

Potential Teratogenicity. Glycoalkaloids have the ability to induce spina bifida, anencephaly (absence of part of the brain and skull), embryotoxicity, and teratogenicity (*236*−*246*). Below are summarized several relevant observations.

Adverse effect on pups associated with consumption of potato sprout-containing diets by pregnant rats that prevented lactation in the dams may be due to the antihormonal effect of solanine (*247*). Feeding of diced potatoes containing 260 mg of solanine/kg of tubers to time-mated rhesus monkeys for 25 days postcopulation produced no maternal toxicity (*248*). By contrast, a single injection of solanine killed the adults within 48 h of treatment. Intraperitoneal administration of α-chaconine or α-solanine to pregnant rats resulted in maternal as well as fetal deaths, but did not induce neural tube defects (*249*). No malformations were found in pregnant rats given continuous intravenous infusion of α-chaconine via implanted osmotic minipumps on days 6−13 of gestation (*250*). The average maternal serum concentration of α-chaconine of 340 ng/mL was about 20 times greater than reported values for humans consuming high-glycoalkaloid potato diets. A study in China (*251*) showed that feeding a glycoalkaloid preparation extracted from potato sprouts to pregnant mice resulted in lethality (LD_{50} = 44.7 mg/kg of body weight) and in embryotoxicity (teratogenicity). Intra-abdominal administration of glycoalkaloids on the fifth or sixth day of gestation induced abdominal bleeding and abortions. Exposure of bovine oocytes during in vitro maturation to 6 μM α-chaconine, α-solanine, or solanidine *N*-oxide inhibited embryo development (*252*).

Pregnant women whose fetuses were subsequently affected by neural tube defects had lower glycoalkaloid serum levels than did another group of pregnant women whose fetuses were not affected (*31*). This result implies that glycoalkaloids do not cause neural tube defects in human fetuses. However, whether the cited data imply that glycoalkaloids at maximum levels normally found in potatoes may not represent a risk of teratogenicity in humans depends on whether pregnant rats and pregnant humans show similar susceptibilities to adverse effects of glycoalkaloids. The apparently contradictory findings imply that the question of whether glycoalkaloids contribute to the incidence of teratogenicity in humans remains unresolved, but may be related to the dosage.

Structure−**Activity Relationships.** The biochemical mechanisms of embryotoxicity, teratogenicity, and neurological impairment are largely unknown. Our own studies on the relative embryotoxicities of 13 test compounds revealed the following (*46*−*48*, *55*): (a) α-chaconine, α-solanine, solasonine, and α-tomatine produced concentration−response curves with α-chaconine being ∼3 times more toxic than α-solanine; (b) glycoalkaloids were more toxic than the aglycons; (c) for glycoal-

kaloids, the nature of the carbohydrate side chains may strongly influence potency; (d) the nitrogen on the steroid ring is required for teratogenicity; (e) orientation of the unshared electron pair associated with the nitrogen does not affect potency; (f) the ring nitrogens are also involved in binding to membrane receptor site; (g) pH influences potency (**Figure 7G**); (h) toxicities observed for individual glycoalkaloids may not be able to predict toxicities of mixtures; (i) the synergism observed for a specific mixture cannot be used to predict possible synergism of other mixtures with different ratios of the two glycoalkaloids; (j) specific combinations found in different potato varieties need to be tested to assess the safety of each cultivar; and (k) the observed structure−activity relationships should facilitate determining and predicting developmental toxicities of dietary compounds without the use of live animals.

Orally induced hamster teratogenicity appears to be more influenced by the presence or absence of C-5, C-6 unsaturation in the alkaloid than by the molecular configuration (stereochemistry) at C-22 and location of the ring N-atom (*253*, *254*).

Absorption, Metabolism, Toxicity. Studies by Gull (*255*), Nishie et al. (*21*, *220*, *221*, *256*), Patil et al. (*257*), Sharma et al. (*217*), and Dalvi (*258*, *259*) [reviewed in Kuiper-Goodman (*260*)] attempted to define the absorption, toxicity, and metabolism of glycoalkaloids in rodents. These findings indicate that biotransformation of the parent glycoalkaloids to the aglycon solanidine and several unknown metabolites takes place both in the digestive tract and in other organs. α-Chaconine and α-solanine behaved similarly with respect to their absorption, distribution, and elimination. Because of poor absorption, rapid excretion, and hydrolysis to less toxic solanidine in the stomach, orally ingested solanine was less toxic than was the intraperitoneally administered compound (*258*). Observed histological effects of the glycoalkaloids included hepatic congestion, leukocytic infiltration, and hepatic tubular necrosis (*217*, *225*).

The sensitivity of hamsters to glycoalkaloids appears to be similar to that of humans (*261*, *262*). Comparison of the bioavailability and disposition of both intravenous or oral administration of [^{3}H]solanine indicates that the hamster is a more appropriate model for subchronic toxicity studies than is the rat (*263*). Observed deaths of hamsters gavaged with potato sprouts were attributed to severe gastrointestinal necrosis and not to inhibition of acetylcholinesterase (*242*).

Reported intraperitoneal (ip) LD_{50} values for mice (in milligrams per kilogram of body weight) for α-chaconine averaged 23; for α-solanine, 34; for solanidine, 500. The oral value for α-solanine was >1000. For rats, the intraperitoneal value for α-solanine was 71 and the oral value, 590. No values have been reported for α-chaconine or solanidine. For rabbits, the ip LD_{50} value for α-solanine was 30 and that for α-chaconine, 50. No oral values have been reported for rabbits. For the rhesus monkey, the ip LD_{50} value for α-solanine was <40. The rat LD_{50} value for α-solamargine was 42 mg/kg of body weight (*264*). These results suggest that LD_{50} values in different animal species appear to be comparable.

Lack of rapid absorption may explain the low toxicity in mice of glycoalkaloids consumed orally (*225*). Data from intraperitoneal and intravenous studies may not measure what actually occurs in the gut after ingestion. Small doses of glycoalkaloids may never enter the blood stream, being used up in binding to cell membranes of the stomach or in binding to other sterols present as part of the diet or undergoing acid or enzymatic hydrolysis. If a high level of a sterol such as cholesterol were ingested simultaneously, the glycoalkaloids could conceivably competitively bind to it rather than to cell membranes.

Disruptive effects on cell membranes in the gastrointestinal tract may be attributed to saponin-like effects that lead to hemolytic and hemorrhagic damage and eventually to septicemia and death (*226*, *227*, *265*). Sleeping times induced by pentobarbital were prolonged by administration of α-solanine (*21*); prior administration of atropine sulfate reduced the mortality rate in mice induced by intraperitoneal administration of solanine (*257*). The extent of binding of [^{3}H]-α-chaconine to mouse hepatocytes was constant when the doses ranged from 1 to 10 mg/kg (*225*). The availability of receptor sites in the liver cells for α-chaconine appears to be limited.

Animal Feeding Studies. Feeding of potato diets (containing 3.08−4.07 mg of glycoalkaloids/kg of body weight/day) to rhesus monkeys for 25 days revealed no adverse effects (*248*). Azim et al. (*222*−*224*) made the following observations during feeding of normal potatoes containing 7.5 mg of glycoalkaloids/100 g and greened potatoes containing 20.4 mg/100 g to rabbits for 20 days. The rabbits on the high-glycoalkaloid diet (49−53 mg/kg of body weight/day) experienced poor protein digestibility, weight loss, and diarrhea, whereas the rabbits that consumed the normal potatoes (20−23 mg/kg of body weight/day) were all normal. The high-glycoalkaloid diets induced a decrease in red blood cell and hemoglobin levels corresponding to hemolytic anemia.

Glycoalkaloid levels of leaves are generally much higher than those in tubers. Because potato leaves form part of the diet of Bangladeshi people, Phillips et al. (*231*) evaluated the composition and toxicities of the leaves in vitro and in vivo assays. These glycoalkaloids were toxic to Chinese ovary hamster (CHO) cells with IC_{50} values (in μg/mL) for α-chaconine of 3.55; α-solanine, 13.8; and the 1:1 mixture of the two, 2.4. The latter value suggests synergistic action of the binary mixture, illustrated in **Figure 8F**. Oral administration of either potato tops or a 1:1 mixture of α-chaconine and α-solanine of up to 50 mg/kg of body weight to rats, mice, and hamsters had no apparent adverse effects. By contrast, a single intraperitoneal injection of 25 mg/kg of body weight caused sudden death. Consumption of moderate amounts of potato tops may not represent an acute health hazard to humans. Because sprouts contain higher levels than do leaves or tubers, consumption of very young potato shoots and sprouted tubers should be avoided.

Feeding glycoalkaloids to mice at levels found in the human diet adversely affected the intestinal tract and aggravated inflammatory bowel disease (*227*). Further studies are needed to establish whether the cited adverse effects are species-dependent.

Liver Effects in Rodents. Hepatic dysfunction in male rats was studied by Dalvi (*259*), who found significant increases in cholinesterase and liver enzyme activities after administration of solanine orally and intraperitoneally. We (*191*) observed dose-related increases in liver enzyme activities in mice fed a normal diet supplemented with several levels of solasodine, the aglycon of solasonine. Mice were fed freeze-dried potato berries (containing 221 and 159 mg/kg of fresh weight of the glycoalkaloids α-chaconine and α-solanine, respectively) at 1, 5, 10, 20, and 40% of the diet, as well as 10% casein diets supplemented with 50−1600 mg of solasodine. All mice fed the 40% potato berry diets died. Solasodine diets induced elevated serum alkaline phosphatase, glutamic-pyruvic transaminase (GPT), and glutamic-oxaloacetic transaminase (GOT); elevated liver weight as a percent of body weight; decreased body-weight gain; and increased incidence of liver cholangiohepatitis and gastric gland dilation/degeneration.

Additional studies revealed that dietary consumption of glycoalkaloids resulted in decreases in mouse liver weights (*208*, *209*). We also determined differences in body weight and liver weight in nonpregnant and pregnant mice, differences in litter size and litter weight, and differences in fetal weight in pregnant mice following dietary exposure to 2.4 mmol/kg of solasodine, tomatidine, or solanidine for 14 days. Dietary administration of 2.4 mmol/kg solanidine to pregnant mice resulted in significantly lower litter size (numbers) (10.2 ± 2.6 versus 12.1 ± 1.9) and lower fetus weights (0.86 ± 0.15 g versus 0.97 ± 0.13 g). Solanidine-induced hepatomegaly was found to be reversible when adult female mice were taken off the alkaloid-supplemented diet. This indicates that hepatomegaly may be a benign adaptive response.

The described liver effects do not appear to be due to genotoxicity of glycoalkaloids because we found the glycoalkaloids to be negative in the in vitro Ames *Salmonella* mutagenicity assay and in the in vivo mouse micronucleus chromosome-damaging bioassay (*266*).

HUMAN STUDIES

Glycoalkaloids, Flavor, and Taste. Consumer acceptance of potatoes is influenced by flavor, taste, texture, and color of potato-based foods. Experiments with human taste panels revealed that potato varieties with glycoalkaloid levels exceeding 14 mg/100 g of fresh weight tasted bitter (*267*, *268*). Those in excess of 22 mg/100 g also induced mild to severe burning sensations in the mouths and throats of panel members. Panelists in a human taste panel detected a slightly bitter aftertaste in some of the small Maori sweet potatoes (kumara) from the genus *Ipomea* native to New Zealand having a glycoalkaloid range from 38.7 to 142.6 mg/kg (*269*).

The Norwegian potato variety Kerrs Pink was quite susceptible to greening-related glycoalkaloid synthesis and accompanying increases in bitterness, whereas the Bintje variety was not (*270*). The diglycoside β_2-chaconine appears to be a potato bitterness factor (*271*, *272*).

A traditional process for the removal of glycoalkaloids from bitter Andean tubers (*Oxalis tuberosa*) grown at low temperatures consists of exposing the tubers to several nights of frost and then drying in strong sunlight at altitudes of 4000 m to obtain black *chuno*. Large bitter potatoes are used to prepare white *chuno*, also called *tunta* or *moraya*. Freezing is followed by peeling, hydrating, and drying to produce an energy-rich dehydrated product (*3*, *4*).

Safety Guidelines for Glycoalkaloids. The major interest in potato glycoalkaloids is due to the fact that several papers have suggested that they may be toxic to humans. Guidelines limiting maximum levels of glycoalkaloids to 200 mg/kg of fresh weight of potatoes are designed to minimize overconsumption of high-glycoalkaloid potatoes. Because glycoalkaloids are present in all commercial potatoes (*32*), they are a widely consumed dietary secondary metabolite. A person consuming 500 g of potatoes may ingest up to 100 mg of glycoalkaloids. The daily per capita intake of glycoalkaloids from potatoes in the United Kingdom is estimated to be ~14 mg (*273*). The concentration can increase postharvest during storage and on exposure of potatoes to light and as a result of mechanical injury [reviewed in detail elsewhere (*274*, *275*)].

The safety of glycoalkaloids for humans is still being debated (*1*, *273*, *276*−*278*). On the basis of the evaluation of information available prior to 1990 on the safety of *Solanum* glycoalkaloids, van Gelder (*81*, *279*) recommended that the accepted guideline limiting glycoalkaloid content of potatoes to <200 mg/kg of fresh weight (an official requirement in many countries but not in the United States) is too high. However, this suggestion may not be justified in view of the more recently discovered synergism between α-chaconine and α-solanine in inducing both adverse and beneficial effects (*55*, *69*, *230*). Because of synergy, it may not be possible to predict the toxicity of a mixture of the two glycoalkaloids using the results of the individual compounds or of mixtures of differing ratios present in different potato varieties. Mixtures can vary in their adverse effects depending on the ratio used. Glycoalkaloids may be either synergistic or additive at one concentration ratio, whereas the interactions may differ at others.

Pharmacology and Toxicology. In several reported cases, death has been attributed to the ingestion of glycoalkaloids from potatoes (*280*), especially from blighted, greened, and sprouted tubers. Potato leaves (*28*) and potato berries (*20*) have also been implicated in fatal poisonings. Other incidents of poisoning have been reported (*281*−*283*). For example, 78 schoolboys became ill after eating lunch (*284*). Investigators traced the problem to potatoes that had "gone bad". The remaining uncooked potatoes contained about 330 mg/kg of glycoalkaloids. Seventeen boys required hospitalization. The common symptoms were nausea, vomiting, diarrhea, abdominal pain, fever, and disorientation. Plasma cholinesterase levels were found to be extremely low. Nobody died, and the symptoms subsided after 1−2 weeks.

Six volunteers developed nausea and diarrhea 1−2 h after eating potatoes containing glycoalkaloids (*285*). Total doses were estimated at 1.7−2.6 mg/kg of body weight. Experiments with seven volunteers gave similar results (*286*). The subjects were given amounts of potatoes containing glycoalkaloids [mashed potato diets containing 200 mg of glycoalkaloids/kg (118 mg/kg α-chaconine and 82 mg/kg α-solanine] corresponding 1.0 mg/kg of body weight for each subject. Six of the seven volunteers experienced a burning sensation of the mouth and light to severe nausea, with one case of diarrhea. Symptoms began after 30 min and lasted for 4 h. The biological half-life of α-solanine was found to be 10.7 h and that of α-chaconine, 19.1 h. Plasma levels ranged from 3 to 11 ng/mL for α-solanine and from 6 to 21 ng/mL for α-chaconine. Solanidine was present at levels below 4 ng/mL. The authors suggest that the rapid onset and short duration of the symptoms may be due to the local effects on the intestine rather than to systemic manifestations.

Livers of human cadavers contained solanidine and glycoalkaloids at levels in excess of 200 ng of glycoalkaloid equiv/g of liver (*287*). Both glycosides and aglycons were detected in the sera of several hundred people who had consumed potatoes (*288*, *289*). Upon cessation of eating potatoes, serum glycoalkaloid levels dropped to 35−55% of initial values after 1 week. Serum levels failed to demonstrate a causal relationship with neural tube defects (*31*).

Morris and Lee (*290*) calculated the actual doses received in several of the older cases and concluded that 2−5 mg/kg of body weight was a toxic dose, whereas a fatal dose was around 3−6 mg/kg of body weight. Actual toxicity may also depend on whether the glycoalkaloids are ingested in small chronic doses or in a larger acute dose, which seems to be more toxic, and whether other potato and dietary ingredients antagonize or potentiate the biological effects of glycoalkaloids. Small potatoes generally contain higher levels of glycoalkaloids per unit of weight than do large ones.

Mensinga et al. (*67*) instituted a clinical trial to evaluate acute toxicity and pharmacokinetics over several days of a single orally administered dose. Subjects 1−3 received one of the

following six treatments: 200-mL solutions of glycoalkaloids consisting of 50% α-chaconine and 50% α-solanine, each containing 0.30, 0.50, or 0.70 mg/kg of body weight. Subjects 4−6 ate mashed potatoes with glycoalkaloid doses of 0.95, 1.10, or 1.25 mg/kg of body weight. The glycoalkaloid level of the mashed potatoes corresponded to 200 mg/kg of fresh weight—the upper safety limit. None of the subjects experienced acute systemic effects. One of the subjects consuming the highest level (1.25 mg/kg of body weight equivalent to 90.2 mg of glycoalkaloids for that subject) became nauseous and started to vomit. The observed slow clearance from the sera, illustrated in **Figure 9A**, suggests a long residence time in the human body and perhaps toxicity due to the cumulative effects associated with long-term consumption of glycoalkaloids. This aspect certainly merits further study. None of the subjects reported a bitter taste.

Figure 9B shows the concentration-dependent hemolysis of human erythrocytes in vitro (*291*). It is not known whether glycoalkaloid-induced hemolysis also occurs in humans in vivo.

Dietary Considerations. We do not know whether glycoalkaloids would induce adverse effects when, as part of a normal diet, they are subject to interaction with other diet components, digestion, absorption, transport, and metabolism. For example, because we do not know whether the oligosaccharide side chains are hydrolyzed in the gut, either by hydrochloric acid or by digestive stomach and liver enzymes, we cannot determine whether the glycosides or the aglycons are the actual toxicants. Only toxicity associated with oral ingestion would give a realistic indication of potential health hazards. Because the structure of the carbohydrate side chain in different glycoalkaloids strongly influences embryotoxicity/teratogenicity in frog embryos, it may also govern potency in animals and humans. Glycoalkaloids are often administered by injection or gavage, so additional studies are needed to ascertain whether the reported findings can be confirmed by parallel oral feeding studies. Possible dietary relationships between glycoalkaloids and other biologically active ingredients present in potato-based diets are largely unknown. These could ameliorate and/or potentiate adverse effects. Such ingredients include secondary metabolites mentioned earlier as well as processing-induced dieatery ingredients. These include degradation products of vitamin C (*292*), browning products (*152*, *293*), lysinoalanine (*294*), D-amino amino acids (*295*), and acrylamide (*119*, *296*, *297*).

BENEFICIAL EFFECTS

Glycoalkaloids and aglycons may also have beneficial effects. A potential cholesterol-lowering effect has been described earlier. Other reported observations are outlined below.

Antiallergic, Antipyretic, and Anti-inflammatory Effects. Treatment with solanine resulted in improvement in 32 patients suffering from allergy to nightshade and cereals (*298*). Crude extracts of the *Solanum linguistrinum* plant containing glycoalkaloids produced antipyretic and anti-inflammatory activities in guinea pigs (*299*). Ethanolic extracts of potato tubers administered orally at doses of 100−200 mg/kg ameliorated pain and inflammation in mice (*300*).

Glycemic Effects of Solanine in Rats. Solanine injected intraperitoneally induced a reversible decrease in blood sugar levels in normal and adrenalectomized rats (*301*). Hyperglycemia appears to be due to stimulation of the adrenal gland by solanine. It was accompanied by a decrease in glycogen levels in the livers.

Antibiotic Activities against Pathogenic Bacteria, Viruses, Protozoa, and Fungi. Numerous foodborne diseases are

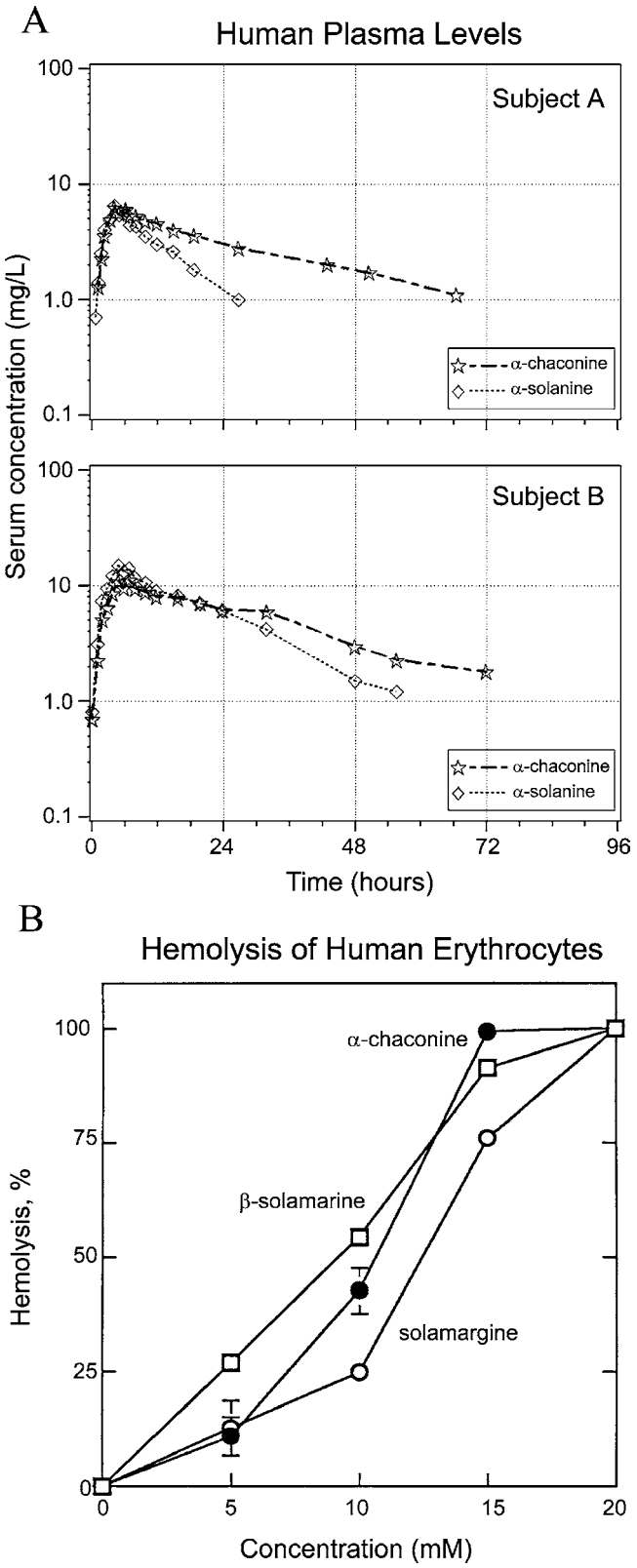

Figure 9. (**A**) Human plasma levels of α-chaconine and α-solanine after consumption of a high-glycoalkaloid potato diet (*67*); (**B**) glycoalkaloid-induced in vitro hemolysis of human erythrocytes (*291*).

syndromes that result from ingesting foods that are contaminated with either infectious microorganisms or toxic substances (toxins) produced by microorganisms. Below are outlined reports that may benefit human health.

α-Chaconine and α-solanine inhibited the growth of *Corynebacterium sepedonicum* (*302*). Mice injected with low levels

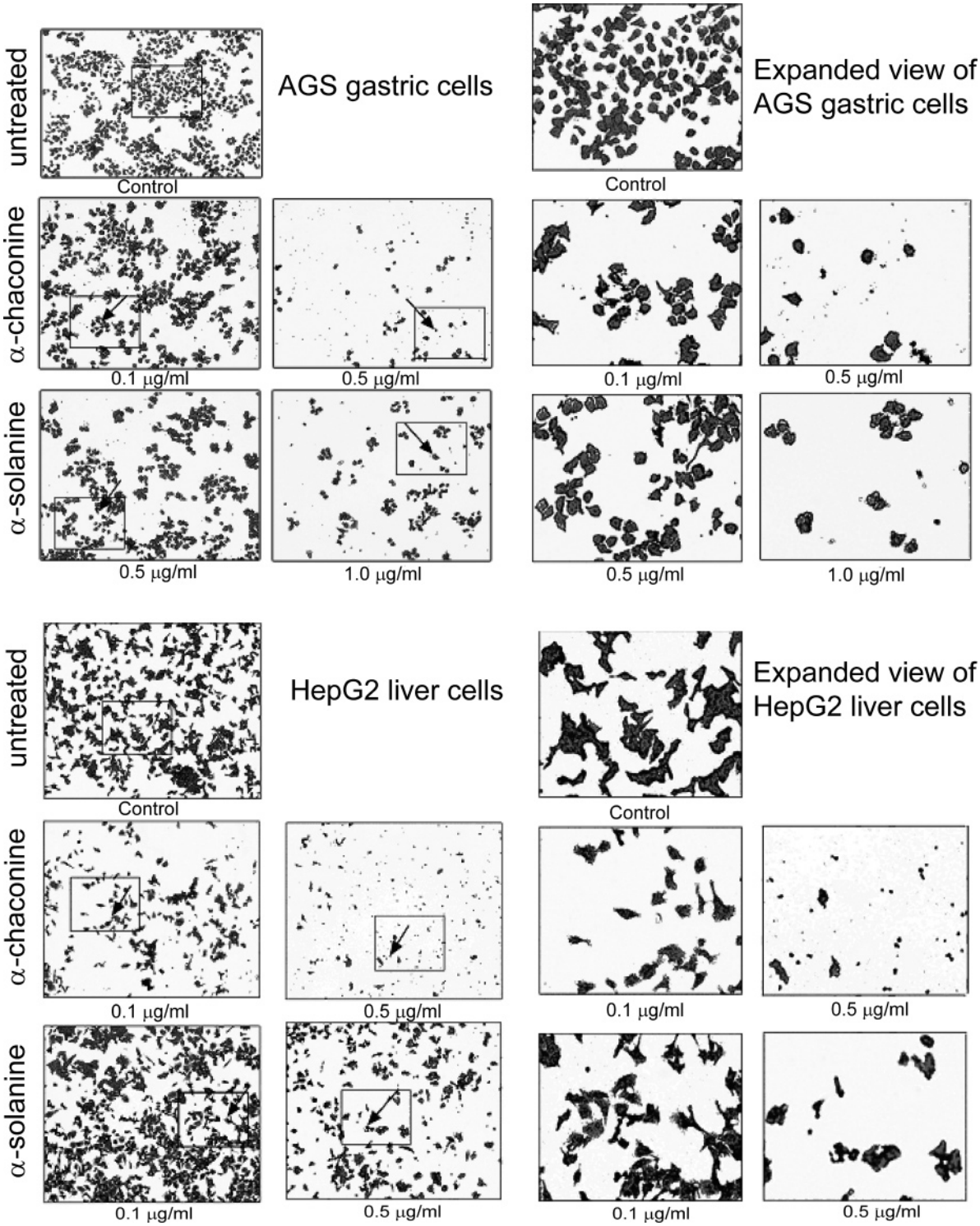

Figure 10. Photomicrographs showing the concentration-dependent destruction of human cancer cells by α-chaconine and α-solanine (*68*, *69*).

of α-chaconine or α-solanine (0.03−0.3 mg/kg of body weight or 0.1−1.0 μg/mouse) were resistant to challenges of lethal doses of *Salmonella typhymurium*. Various organs of treated mice were clear of bacteria (*70*, *71*). The protective effect may due to enhancement of host resistance to microbial infection by the bioactive plant glycoalkaloids, possibly by stimulation of the innate immune system, in analogy to that observed with tomatine (*2*). α-Chaconine, α-solanine, solasonine, or tomatine inhibited *Herpes simplex* virus in tissue culture (*303a*,*b*). The corresponding aglycons solanidine, solasodine, and tomatidine were inactive. A cosmetic cream formulation containing solamargine and solasonine from *Solanum americanum* reduced lesions in patients with *Herpes genitalis*, *Herpes simplex*, and *Herpes zoster* (*304*). These lesions did not recur in most patients up to 9 months following treatment. Viral inhibition may due to insertion of the glycoalkaloids into the viral envelope.

A preparation form *Solanum nigrescens* leaves inhibited the fungus *Candida albicans* in vitro and vaginal candidiasis in guinea pigs and in infected women (*305*). Micromolar levels of α-chaconine and solamargine inhibited protozoa in culture (*306*). The presence of rhamnose in the carbohydrate moiety appears to strongly influence activity, which is the result of membrane disruption and dissolution of protozoan organelles. We do not known whether glycoalkaloids would inhibit

pathogens that contaminate potatoes (*307*) and whether orally consumed glycoalkaloids would protect against infectious diseases.

Destruction of Human Cancer Cells. We evaluated glycoalkaloids and hydrolysis products for their ability to inhibit the growth (antiproliferative activities) of human colon (HT29) and liver (HepG2) cancer cells using a microculture tetrazolium (MTT) assay (*68*, *69*). Comparative evaluations were carried out with four concentrations each (0.1, 1, 10, and 100 μg/mL) of the potato glycoalkaloids α-chaconine and α-solanine; β_1-chaconine, β_2-chaconine, γ-chaconine, and their common aglycon, solanidine; the eggplant glycoalkaloids solamargine and solasonine and their common aglycon solasodine; the tomato glycoalkaloid α-tomatine and its aglycon tomatidine; and the aglycon demissidine. All of the test compounds inhibited growth of the tumor cells (**Figure 10**). Activity was influenced by the chemical structurd, the number of carbohydrate groups making up the side chain attached to the aglycons, and the structure of the aglycon. The relative potency of the anticancer drug adriamycin against the liver cancer cells was similar to those observed with α-tomatine and α-chaconine.

Because some combinations of α-chaconine and α-solanine can act synergistically in lysing cell membranes (*55*, *232*), we wanted to find out whether this is also true for cancer cells. **Figure 8A** illustrates a theoretical isobole diagram designed to establish the existence of additive, antagonistic, or synergistic interactions. Such a plot shown in **Figure 8B** indicates synergy in the malformation of frog embryos and, in **Figure 8C**, synergy against human cancer cell. Synergy was also observed in the inhibition of snail feeding (**Figure 8D**), cholesterol binding (**Figure 8E**), and inhibition of Chinese ovary hamster cells (**Figure 8F**).

Our observations complement previous studies which showed that (a) the glycoalkaloid β-solamarine present in the folk medicine *Solanum dulcamara* inhibited sarcoma tumors in mice (*308*); (b) solamargine and solasonine isolated from *Solanum sodomaeum* were effective treatments of malignant human skin tumors including basal and squamous cell carcinomas (*309*); (c) solamargine and solasonine exhibited preferential toxicity for human cancer cells compared to other cell types (*310*); (d) solamargine present in *Solanum nigrum* was cytotoxic to six cultured human solid tumor cell lines (*311*); (e) the anticarcinogenic action of solamargine, α-chaconine, and solanine is the result of cell death by apoptosis (programmed cell death) (*312*−*315*); (f) tomatidine inhibited the resistance of cancer cells to drugs (*316*); (g) solasonine, present in *Solanum crinitum* and *Solanum jabrense*, was cytotoxic against Ehrlich carcinoma and human K562 leukemia cells (*317*); and (h) the rhamnosyl sugar in the carbohydrate side chain strongly influenced the cytotoxicity of glycoalkaloids (*318*).

Because humans may consume at least six glycoalkaloids in their diet (α-chaconine and α-solanine from potatoes; α-tomatine and dehydrotomatine from tomatoes; and solamargine and solasonine from eggplants), there is need to further define possible beneficial effects of combinations of dietary glycoalkaloids against cancer cells and tumors. Effectiveness as well as safety considerations should govern the dietary consumption of glycoalkaloids.

SUMMARY AND OUTLOOK

Potato glycoalkaloids may have evolved in nature to protect the plant against phytopathogens and other hostile environments. On the basis of the cited data we have discussed in this review, our current knowledge of plant physiology and the biology of these secondary metabolites is incomplete. In addition to research needs mentioned earlier, plant scientists are challenged to define the gene transcription mechanisms and control of the biosynthesis, metabolism, and degradation of glycoalkaloids as well as to further assess possible synergistic effects against phytopathogens of different ratios of α-chaconine and α-solanine found in different cultivars. It may be that the specific ratios of α-chaconine to α-solanine that exhibit synergism are more important than total levels in protecting plants against phytopathogens. Potato strains should be developed with reduced amounts of the most toxic glycoalkaloids and metabolites while maintaining resistance to phytopathogens. Food and biomedical scientists, including nutritionists, pharmacologists, and microbiologists, are challenged to further define the beneficial effects of the glycoalkaloids against cancer, the immune system, cholesterol, and inflammation, as well as against pathogenic fungi, bacteria, viruses, and protozoa. An unsolved question is whether orally consumed glycoalkaloids are teratogenic for primates and humans. Long-term feeding studies with primates may help to resolve this long-standing puzzle.

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