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Chapter

# Food Glycoalkaloids: Distribution, Structure, Cytotoxicity, Extraction, and Biological Activity

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## Abstract

Glycoalkaloids (GA), generally occur as plant steroidal glycosides, are secondary metabolites produced in the leaves, flowers, roots, and edible parts including sprouts and skin of the plants of *Solanaceae* family. Many of the plants in this family have been stable parts of human diets for centuries, and thus, the occurrence of these compounds has been extensively studied mainly due to concerns regarding their toxicity. GAs are produced by plants as a resistance to challenges such as insects and pests but may also produce concentration-dependent toxic effects in humans. Postharvest conditions such as light, temperature, humidity, and processing conditions may also affect GA content in edible plants producing them. Since these compounds also possess biological properties such as anti-inflammatory, antimicrobial, and anticarcinogenic activities, it could be a useful strategy to use novel extraction techniques to maintaining bioactivities after extraction and simultaneously to reduce toxicity in the source plants. This chapter aims to describe alkaloids especially GAs commonly occurring in foods, their structure and toxicity, and postharvesting practices which influence alkaloid content and utilization of conventional and novel technologies to extract food alkaloids.

**Keywords:** food glycoalkaloids, aglycones, α-solamargine, α-solasonine, solasodine, α-chaconine, α-solanine, solanidine, α-tomatine, tomatidine, cytotoxicity, food safety, anticancer, novel technologies

## 1. Introduction

Plant uses complex biochemical pathways to produce secondary metabolites to tackle adverse environmental stimuli such as damages from herbivores, pathogens, or deprivation of nutrients. These secondary metabolites can be species- or genera-specific and generally do not serve any role in the growth and development of the plants but improve plant viability by increasing their overall ability to cope with the local environmental challenges [1]. Apart from protecting the plant from bacteria, fungi, and viruses, some of the secondary metabolites function as radical-scavenging, UV light-absorbing, and antiproliferative agents [2]. Plants produce a large number of secondary metabolites which, based on their biosynthetic origins, are divided into three major groups: terpenoids, phenolic compounds, and alkaloids [3].

Among plant secondary metabolites, GAs are interesting not only for chemical and biological reasons, but also because they have exerted an important influence on various aspects of human activity and behavior [4]. GAs are steroidal alkaloids that usually possess a sterol skeleton in six heterocyclic rings with a nitrogen. These GAs work as a part of the defense system in many plants including widely consumed agricultural plants of *Solanaceae* family such as potato (*Solanum tuberosum*), tomato (*Solanum lycopersicum*), and aubergine (*Solanum melongena*). Solanine was considered the only compound of this type present in potatoes until chaconine was discovered in 1854. Tomatine, which was in fact the mixture of

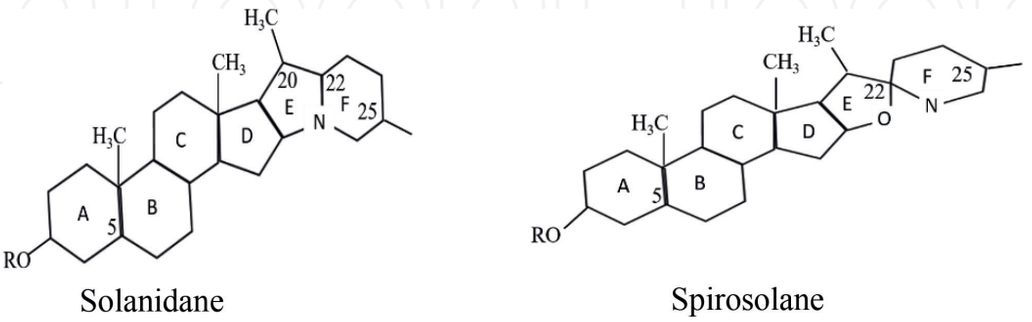



**Figure 1.**
*Structures of solanidane and spirosolane glycoalkaloids (taken from [4]).*

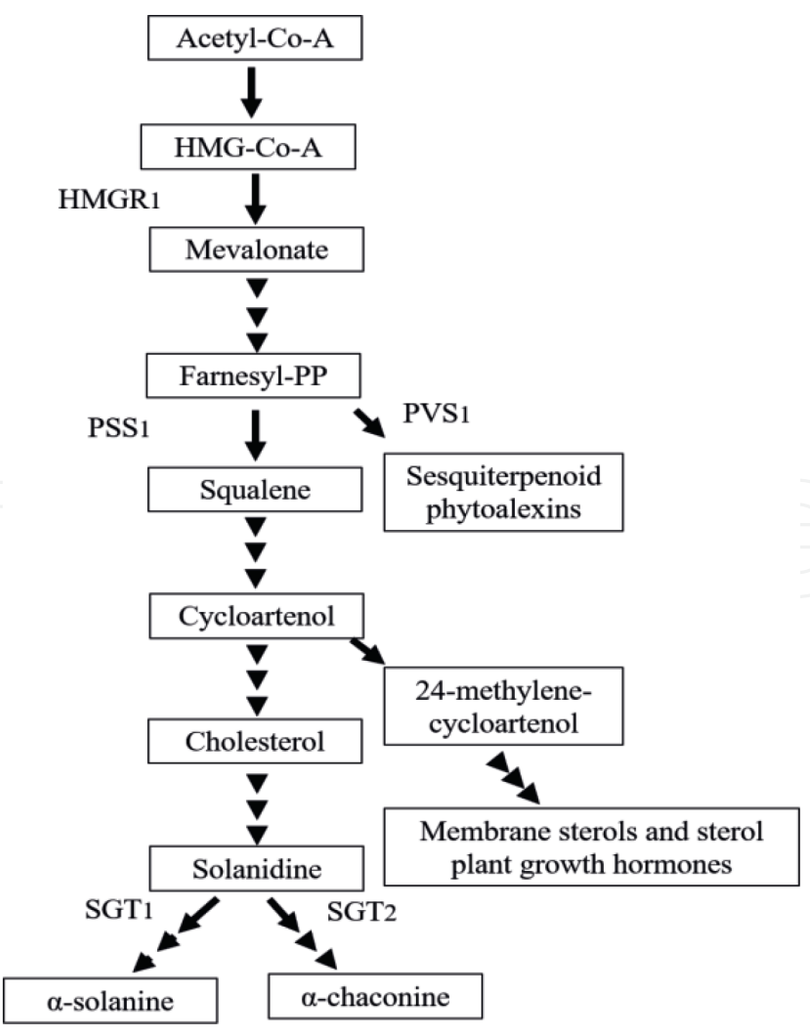



**Figure 2.**
*Schematic representation of proposed steroidal GA biosynthesis. Triple arrowheads represent several enzymatic steps (taken from [11]).*

tomatine and dehydrotomatine, was discovered in tomato in 1948. The major GAs of aubergine, solasonine, and solamargine were discovered later and found in 100 other species [5].

Plants often contain alkaloids in glycosidic form as GAs. GAs consist of two structural components: an aglycone structure which is based on C27 cholestane skeleton with an additional nitrogen-containing rings that impart the basicity and oligosaccharide moiety making GAs amphiphatic in nature. The aglycones are divided into five different categories depending on their structure: solanidanes (with fused indolizidine rings), spirosolanes (with an oxa-azaspirodecane alkaloid portion) [6, 7], epiminocholestanes, α-epiminocyclohemiketals, and 3-aminospirostanes [8]. Based on the skeletal type of the aglycone, plant steroidal GAs vary as spirosolan types, similar to spirostan, but with nitrogen in place of the oxygen in ring F and another is the solanidane type, where nitrogen connects spirostan rings E and F (**Figure 1**) [9]. At least, 90 structurally unique steroidal alkaloids have been identified in over 350 *Solanum* species. Nitrogen can be attached as a primary $NH_2$ group in position 3 or 20 (free or methylated), forming simple steroidal bases (e.g., conessine), ring-closed to skeletal or side-chain carbon (as a secondary NH), or annelated in two rings as a tertiary N (e.g., solanidine). This often influences the chemical character of the compound [10]. In addition, a significant portion of the biological activity of GAs derives from the oligosaccharide moieties [4].

Relatively, little is known about the biosynthetic pathway of steroidal glycoalkaloids and the factors that regulate GA levels in plants. However, the aglycone of the steroidal GAs is assumed to be synthesized via the mevalonate/isoprenoid pathway (**Figure 2**). The enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGR) catalyzes the first step specific to isoprenoid biosynthesis. Downstream, squalene synthase (PSS1), and vetispiradiene (sesquiterpene) cyclase (PVS1) catalyze the first steps in the branches leading to sterols, steroidal GAs, and sesquiterpenoid phytoalexins, respectively [11].

## 2. Distribution of GAs in different plants

### 2.1 Potato plants

Historically, solanine was the first alkaloid to be isolated from the potatoes [12] and recognized as a glycoside. However, lately, it has been shown that solanine actually was a mixture of two components namely α-solanine and α-chaconine [13]. The two major GAs present in potato (*Solanum tuberosum*), α-solanine and α-chaconine, share the same aglycone, solanidine, but differ with respect to the composition of the sugar side chain (**Figure 3**). α-Chaconine is composed of a branched β-chacotriose (bis-α-L-rhamnopyranosyl-β-D-gluco-pyranose) carbohydrate side chain attached to the 3-OH group of the aglycone, whereas α-solanine has a branched β-solatriose

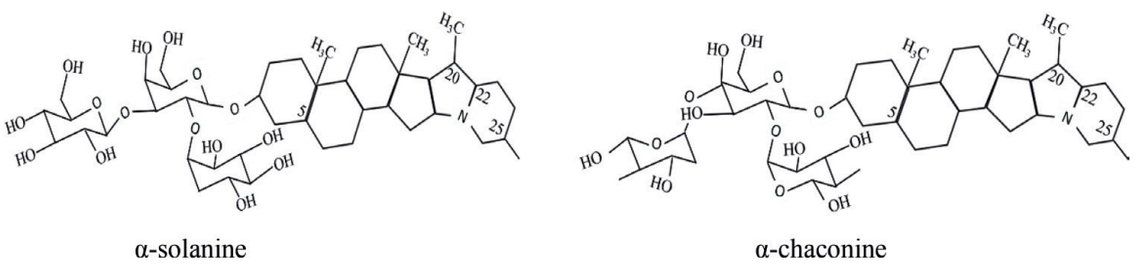



**Figure 3.**
*Structure of two major GAs from potato (adapted from [5]).*

(α-L-rhamnopyranosyl-β-D-glucopyranosyl-β-galactopyranose) side chain also attached to the 3-OH group of the same aglycone. Potatoes may contain small amounts of the hydrolysis products, (β- and γ-chaconines, β- and γ-solanines) solanidine [14].

Apart from commercial varieties α-solanine and α-chaconine, other GAs may also be present in wild species. For example, the leaves and stems of *S. chacoense* contain leptines and leptidines, steroidal alkaloids in addition to the α-solanine and α-chaconine [15]. High levels of GAs are found in potato tissues which undergo intensive metabolic processes, that is, fruits, leaves, stems, tubers eyes, jacket, sprouts, and damaged tissues [16, 17]. While, the GA level associated with the potato sprouts is generally conceded to be higher than that of the rest of the tuber [18]. However, environmental conditions including infection from fungal pathogens and other factors such as climate, soil type, soil moisture, etc., can lead to an increase in the amount of TGA present in any tissue [19]. It has been reported that potato tubers normally contain 1–15 mg/100 g fresh weight of the GAs α-solanine and α-chaconine. Elevated levels of GAs are normally found in potato peels although it should be noted that the peel comprises less than 20% of the total tuber weight [20]. Dao and Friedman [21] used an HPLC assay to determine the amount of α-solanine and α-chaconine in fresh potato leaves at various levels of maturation (from 1 to 9 weeks) in two different potato varieties and found that α-chaconine increased from 20.2 (3 weeks) to 111.4 mg/100 g fresh weight (9 weeks) and α-solanine increased from 9.6 to 50.1 mg/100 g fresh weight over the same period. In another study, Brown et al. [22] showed that the GA content increased with the leaf maturity and then declined with further age when analysis was performed with leaf samples on the same day. Although the amount of GA in potatoes depends on many different factors, **Table 1** gives a good approximation of the ranges that have been reported.

## 2.2 Tomato plants

About 100 steroidal alkaloids have been found in different tissues and development stages of the tomato plant [24–26]. Tomato plants (*S. lycopersicum*) contain the spirosolane-type GAs α-tomatine and dehydrotomatine (**Figure 4**). The presence of a double bond in the steroidal ring B in structure of dehydrotomatine is the distinguishable feature between α-tomatine and dehydrotomatine. Both of the GAs

| Potato part | Total GAs (mg/kg fresh weight) |
|---|---|
| Tuber with skin | 75 |
| Tuber with skin (bitter taste) | 250–800 |
| Peel (skin) | 150–600 |
| Peel (skin) from bitter tuber | 1500–2200 |
| Tuber without skin | 12–50 |
| Sprouts | 2000–4000 |
| Flower | 3000–5000 |
| Stems | 30 |
| Leaves | 400–1000 |

*Taken from [23].*

**Table 1.**
*Distribution of GA in potatoes.*

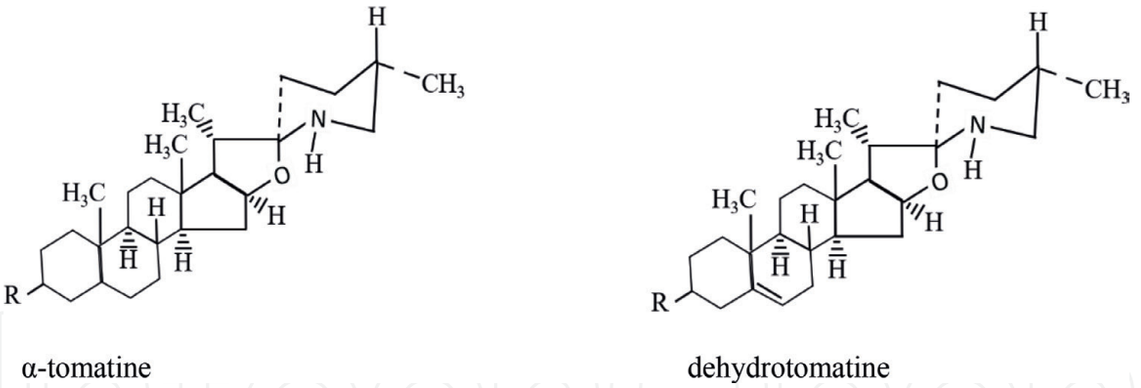



**Figure 4.**
*Structure of α-tomatine and dehydrotomatine (taken from [28]).*

have same tetrasaccharide side chain (lycotetraose), but they differ in the aglycone structure. α-Tomatine has lycotetraose attached to the aglycone tomatidine, whereas dehydrotomatine has lycotetraose attached to the aglycone tomatidenol [27].

All parts of the tomato plant including leaves, stems, and tomato fruits contain tomatine and dehydrotomatine. Immature green tomatoes contain up to 500 mg α-tomatine/kg of fruit weight. However, tomatine is largely degraded as the fruit ripens, to a level of only 5 mg/kg of fresh fruit weight in red tomatoes [29]. While unripe green tomatoes contain tomatine and dehydrotomatine, isolation of another major spirosolane-type glycoside esculeoside from mature cherry tomato has also been reported by Fujiwara et al. [30]. However, these authors concluded that esculeosides A and B might be produced from the tomatine in the immature tomato as tomato matures. Again, a wide range of levels of GAs have been reported in the different parts of the tomato plant; however, **Table 2** presents a good approximation of the levels reported.

## 2.3 Eggplants

Solasonine and solamargine are two major steroidal alkaloids found in eggplant (*Solanum melongena*) (**Figure 5**). These two GAs have the same aglycone (solasodine), but differ in the nature of the trisaccharide side chain. The trisaccharide side chain of solasonine is solatriose, whereas chacotriose is the trisaccharide attached to

| Tomato plant part | Dehydrotomatine (mg/kg fresh weight) | α-Tomatine (mg/kg fresh weight) |
|---|---|---|
| Large immature green fruit | 14 | 144 |
| Small immature green fruit | 54 | 465 |
| Roots | 33 | 118 |
| Calyxes | 62 | 795 |
| Leaves | 71 | 975 |
| Small stems | 138 | 896 |
| Large stems | 142 | 465 |
| Flowers | 190 | 1100 |
| Senescent leaves | 330 | 4900 |

*Adapted from [5].*

**Table 2.**
*Distribution of GA in tomato fruits and plants.*

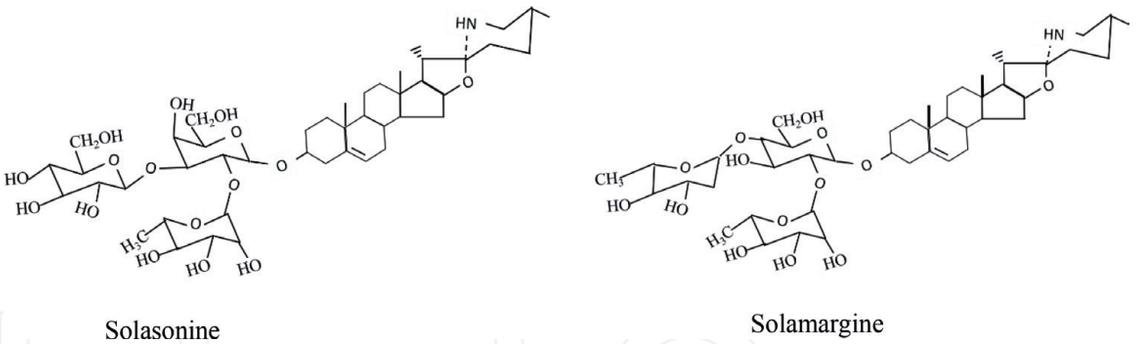



**Figure 5.**
*Chemical structure of solasonine and solamargine (taken from [34]).*

the solasodine aglycone of solamargine [31]. Eggplant GAs differ from those found in major potato alkaloids (α-chaconine and α-solanine) only in the structure of the steroidal part of the molecules, while having identical carbohydrate side chains attached to the aglycone structure. Generally, the GAs solamargine and solasonine are found in the fruits of eggplant. A study of 10 eggplant lines and the 3 allied species (*S. aethiopicum*, *S. integrifolium*, and *S. sodomaeum*) confirmed that the allied species had higher GA content than the widely consumed eggplants and that the GA content generally increased during fruit development and ripening [32]. A calorimetric study of 21 different varieties of *S. melongena* as carried out by Bajaj et al. showed GA content ranged from 6.25 to 20.5 mg/100 g fresh weight (mean value 11.3 mg/100) [33].

## 3. Human and animal toxicity

None of the *Solanace*ous crops consumed as vegetables are toxic if standard cultivation/production practices are adhered to. However, factors associated with the growth, harvest, and postharvest practices, high temperatures, and wounding may elevate GAs to toxic levels [35]. Several other environmental stresses as well as maturity level and the use of fertilizer can also influence the amount of GA [18]. For example, a significant increase in GA concentration has been reported in potatoes cultivated in drought stress conditions where average concentration increases of 43 and 50% were reported in the improved and control cultivars, respectively [36]. Unusually, cold and wet conditions during potato tuber development and growth have often been assumed as a cause of high glycoalkaloid levels [37]. However, hot and dry conditions during plant growth have also been suggested to be responsible for increasing glycoalkaloid concentrations [38, 39]. It is important for human safety to keep steroidal GA levels as low as possible in edible organs of these crops [16]. Some of the toxic effects of GAs are attributed to direct inhibition of cholinesterase activity and more general cell membrane disruption mediated via interactions between membrane sterols and the steroidal moiety of the steroidal GAs [40–42]. Furthermore, interactions between membrane budding and increased permeability may result in a loss of ion conductivity of the cells [43, 44]. Excessive consumption induces gastroenteritis, gastrointestinal discomfort, diarrhea, vomiting, fever, low blood pressure, fast pulse rate along with neurological and occasional death in human and farm animals [45].

The toxicity of solanine depends on the species and route of administration. Parenteral administration is much more toxic than oral administration. Gastrointestinal effects may occur at relatively low levels of exposure such as lower than 2 mg total GA/kg body weight. The biological half-life of α-solanine is about

21 h; it disrupts the membrane of red blood cells and other cellular membranes and exhibits poor absorption in the gastrointestinal tract, its highest distribution is in spleen, but levels in blood become greatest after about 5 h [46, 47]. Therefore, accumulation of GAs in the body may occur which eventually can lead to adverse health effects [47]. Patil et al. reported that i.p. administration of α-solanine to mice induced irritation for about 1 min and the animals were quiet and appeared to be sleepy and apathetic, exhibiting more rapid breathing, hind leg paralysis, and dyspnea [48]. While α-chaconine is considered more toxic than α-solanine, a combination of both of these GAs can induce a synergistic toxic effect. α-Chaconine has a half-life of about 44 h, longer than that of α-solanine [47]. In mice, the i.p. $LD_{50}$ was reported to be 27.5 mg/kg, and in rabbits, the lowest lethal dose was 50 mg/kg i.p. [49].

Although tomatine also alters cell membranes [50], its oral toxicity is low when compared to other GAs, presumably because its cholesterol complex is not absorbed from the gut [51]. The amount of α-tomatine in the tubers of somatic hybrids in tomato and potato has been reported to be 5- to 10-fold higher than those in their parents [52], and these levels could pose a health threat if consumed by humans. Unripe green tomatoes are routinely consumed as fried vegetables or as pickles, and fruits "turning" from green to red are preferred raw by some consumers. Overconsumption of such fruit poses a potential health risk due to α-tomatine toxicity [16]. According to Roddick, lethality occurred within 0.5–2 min in mice, to which α-tomatine was administrated intravenously at a level of 18 mg/kg of body weight. The most common responses to intravenous α-tomatine administration are a large decrease in blood pressure and fluctuations in respiratory rate. Where the dose of α-tomatine was lethal, death was thought to be due to a drop in blood pressure, but with sublethal doses, the initial drop was followed by an equally rapid recovery [53].

Only a few studies concerning the toxicity of solamargine have been published. However, a study conducted by Zheng et al. reported that the biotransformation of solamargine is relatively quick. Eight hours after an intravenous administration of 4 mg/kg to rats, only a trace amount of solamargine could be detected [54].

## 4. Postharvest technologies that influence the amount of GAs

A number of factors influence the formation of GA's preharvest, during harvest, and postharvest. These factors can be summarized as follows:

1. potato cultivars and environmental and growing conditions;

2. maturity during harvesting time, temperature during growth, and extent of sprouting;

3. any mechanical damage such as bruising, cutting, wounding, and slicing that has occurred during handling;

4. postharvest storage conditions in particular wavelength, duration, and intensity of light during storage;

5. other environmental conditions during packaging, transportation, and marketing [55–57].

Considerable research has been performed on potato storage conditions such as temperature, time, and light, and it has been found that these conditions have a

profound impact on the GA level of potatoes. Scientific reports on the effect of temperature on potato GAs are however somewhat conflicting. For example, one study reported a twofold higher level of GA in potato tubers after 6 weeks storage at 4–6°C compared to those stored at 12–15°C [58]. The amount of GA has also been reported to increase at 10°C, while further decreasing the temperature to 4.4°C resulted in only a minor change [59]. A rise in the solanine content in tubers stored at high temperatures was also reported by Salunkhe et al., who found small increase in potato stored at 0 and 8°C and much greater increase in those stored at 15 and 24°C. These authors concluded that the increase may be related to a stress response [60].

The amount of GAs can also vary as a result of exposure to varying light sources such as daylight, UV, fluorescent, and incandescent light during harvesting, storage, and transportation [61]. For example, Machado et al. investigated the effect of different light sources and temperature on the level of GAs in potato tubers. Their investigation involved exposing potato tubers (cv Monaliza) to a range of conditions such as indirect sunlight, fluorescent light, storage in darkness under refrigeration, and storage in darkness at room temperature for 14 days. Potato tubers exposed to fluorescent light had the highest GA levels. Increases in GA levels in lower size potato tubers stored under indirect sunlight and fluorescent light were approximately 4–6 times greater than that of potato tubers stored in darkness at room temperature [58]. Similarly, Salunkhe et al. reported that exposure to sunlight or artificial light can increase GA synthesis in potatoes by factors of 3 or 4 compared to those of potatoes stored in the dark [60]. Other authors have reported that the blue spectral portion (<500 nm, especially UV light <300 nm) and infrared light (1300 nm) are active elicitors of GAs synthesis; while light of 570–700 nm enhances chlorophyll but not GA synthesis [62]. For storing potatoes for a longer period, it is necessary to choose unwounded and ungreened potatoes, and to store in the dark at 5–8°C to prevent sprouting and a corresponding increase in GA content.

It has been reported that domestic cooking and processing such as boiling, baking, and frying does not reduce the amount of GAs in potatoes. The cooking of potatoes has variable effects since GAs are very heat stable, with solanine decomposing at temperatures between 260 and 270°C [63]. While boiling of potatoes does not affect the level of GAs, there are some reports that microwaving could reduce this amount. For example, in a study conducted by Takagi et al., a reduction of alkaloid content by 15% was reported following microwaving, whereas boiling lowered the α-chaconine and α- solanine content by 3.5 and 1.2%, respectively [64]. However, since GAs are localized near the skin (usually no deeper than 3 mm), peeling deep enough to remove any green layer will remove most of the GAs [65]. In most potatoes, the peel contains 60–80% of GAs [66], while for bitter-tasting potatoes, this amount was found to be 30–35% [67]. Generally, chips and fries are considered to be nonhazardous as processing involves the removal of the peel of the potatoes. Potatoes are a versatile commodity and this is reflected in the range of products for which GA levels have been measured by other authors as presented in **Table 3**.

Generally, tomatine is quite stable in food; studies, however, have shown that some products based on unripe green tomatoes lost a considerable amount of tomatine during prolonged storage [69, 70]. Cooking for a shorter time (5 min) had a marginal effect, while considerable losses of tomatine (90–95%) were observed during storage of freeze-dried products at room temperature for 4 weeks, the loss being greater for whole tomatoes than for pulp [69]. Storing green tomato fruits, containing 90 mg tomatine/kg of fresh weight (1040 mg/kg dry weight), for up to 170 days at −20°C as a freeze-dried product, after pulping and sterilization at 121°C for 30 min, and preserved with benzoic acid resulted in an increase in the content of tomatine for all products during the first week of storage and a decrease thereafter. After 50 and 170 days storing, the content of tomatine was reduced to

| Product of preparation | GA concentration (mg/kg product) |
|---|---|
| Boiled peeled potato[a] | 27–42 |
| Baked jacket potato[a] | 99–113 |
| Chips (US: French fries) | 0.4–8 |
| Chips (UK) | 19–58 |
| Oven chips (UK) | 27–86 |
| Fried skins | 567–1450 |
| Frozen mashed potato | 2–5 |
| Frozen baked potato | 80–123 |
| Frozen chips | 2–29 |
| Part cooked frozen chips | 23–55 |
| Precooked frozen chips | 19–35 |
| Frozen skins | 65–121 |
| Frozen fried potato | 4–31 |
| Canned peeled potato | 1–2 |
| Canned whole new potato (tubers) | 24–34 |
| Canned whole new potato (liquor) | 15–17 |
| Canned potato (UK) | 29–99 |
| Crisps (US: potato chips) | 23–180 |
| Crisps (UK: potato chips) | 32–184 |
| Crisps (Norwich) | 59–70 |
| Crisps (with skin) | 95–720 |
| Dehydrated potato flour | 65–75 |
| Potato powder | 39–135 |
| Dehydrated potato flakes | 15–23 |

*Taken from [68].*

[a]*Noncommercial preparation.*

**Table 3.**
*Levels of GA in various commercial potato products and preparations.*

around 60 and 20 mg/kg dry weight in all products [70]. In a review, Friedman and Levine mentioned the average amount of α-tomatine present in a half-cup (125 g) of condensed tomato soup, one table spoon of ketchup (15 g), and 6 fl oz. (183 g) of juice as 0.2, 0.13, and 0.5 (mg)/serving, respectively. Other tomato products, such as half fruit of green pickled (40 g), contain 2.9 mg, while 133 g of fried green tomato contains 1.5 mg of tomatine/serving size [71].

## 5. Anticancer activity

The ability of SGAs to disrupt cellular structure has been examined by some researchers as a possible application of these compounds for treating cancer cells. Extracts obtained from *Solanum* spp. have been used to treat cancer for centuries and there are some indications that they possess cytotoxic activity. For example, α-solanine was found to have a proliferation-inhibiting and an apoptosis-promoting effect on multiple cancer cells, such as clone, liver, melanoma cancer cells [72]. Friedman et al. [73] examined the impact of GAs extracted from one potato variety

and mixtures of GAs extracted from five different widely consumed commercial potato varieties in Korea and Japan on a number of cancer cell lines. They reported a reduction in the numbers of the following cell lines: cervical (HeLa), liver (HepG2), lymphoma (U937), stomach (AGS and KATO III) cancer cells, and normal liver cells and that this effect was concentration dependent (0.1–10 μg/ml) with α-chaconine being more effective than α-solanine. Ji et al. observed induction of apoptosis in the HepG2 cell line from the digestive tracts using the MTT assay and screening the sensitive cells and then measuring the morphological changes of the tumor cells. These authors observed that sub-$G_0$ apoptosis peaks at different doses of solanine and that a decrease in the content of antiapoptotic protein was dose dependent. In pancreatic cancer cells, a nontoxic quantity of solanine (3, 6, and 9 μg/μl) inhibited metastasis (*in vitro*), such as invasion, migration, and angiogenesis, which demonstrated that the inhibitory effect of solanine on metastasis was via its cytotoxic activity. In these cancer cells, α-solanine stimulated p53 and Bax but also suppressed Bcl-2, which led to a release of cytochrome *c* within the mitochondrial pathway of apoptosis. The decrease in Bcl-2 and increase in Bax were also demonstrated in cancer tissue [74]. An increase in proapoptotic Bax protein in breast cancer tissue in mice treated with α-solanine was shown by Mohsenikia et al. [75].

However, several other studies have shown that α-solanine can lead to cancer development and metastasis suppression through inhibition of vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs) [76]. MMPs are believed to participate in tumor cell migration, tissue invasion, and metastasis [77]. In another study, Pan et al. noted α-solanine-induced prostate cancer cell inhibition through the suppression of cell cyclin proteins and through the induction of reactive oxygen species and activation of P38 MAPK pathway [78]. Another effect of α-solanine in cancer cells is the inhibition of cell migration and invasion caused by inhibition of the phosphorylation of JNK, PI3 K, and Akt and, thus, the inhibition of MMP-2 and -9 expressions. In addition, a downregulation of the nuclear content of NF-κB was demonstrated in α-solanine-treated cells [79]. Furthermore, Lee et al. investigated the role of potato GAs such as α-chaconine and solanine and their hydrolysis products at four concentrations (0.1, 1, 10, and 100 μg/mL) on the human colon (HT-29) and liver (Hep G2) cell lines. Results showed that α-chaconine was more effective on both of the cell lines, the inhibition of both cell lines increased with the concentration but did not appear to be in a linear function of the concentration and the inhibition of the liver cells was greater than that of colon cells. The hydrolysis product of α-chaconine, that is, *γ*-chaconine exhibited low activity against the colon cells in contrast to the high activity against the liver cells. The activity of γ-chaconine against the liver cells was greater than those mentioned for *β1*- and *β2*-chaconine and approached that of α-chaconine. In the case of α-solanine, the inhibitory activity at the 100 μg/mL level was similar for both cell lines and the inhibition at a reduced concentration was lower than that of α-chaconine. These results suggest that the nature and presence of the carbohydrate moiety can affect cytotoxicity [80].

Recently, the anticancer effect of α-tomatine and its mechanism of action have been studied. It has been proposed that tomatine can kill cells by binding to cell membranes followed by leakage of cell components [81]. Binding of tomatine to cholesterol may be relevant to the mechanism of inhibition of carcinogenesis. Despite the ability to disrupt cell membranes *in vitro*, orally consumed tomatine is not toxic, presumably because it forms an insoluble complex with cholesterol in the digestive tract, which is then eliminated in the faces [82]. In addition, Sucha et al. observed an inhibition in MCF-7 human breast adenocarcinoma cell line proliferation and viability at α-tomatine concentrations from 6 to 9 μM and postulated that the cytotoxic mechanism could be due the fact that cholesterol in biological membranes serves as a target for the α-tomatine [83]. It has also been reported

that α-tomatine suppresses cell adhesion, morphology/actin cytoskeleton arrangement, invasion and migration in human nonsmall cell lung cancer NCI-H460 cells. The authors compared of 0 μM, after 24 and 48 h treatment with tomatine at a concentration between 0 and 1.5 μM and reported no significant alteration of cell viability, indicating that the compound is not toxic to NCI-H460 at these dosages. However, cell viability was significantly decreased when the applied concentration of tomatine was increased to 2–4 μM for 24 and 48 h [84]. Furthermore, α-tomatine induced a significant cytotoxic effect on the human leukemia cancer cell line HL60 and K562. Experiments using the MTT assay revealed that tomatine has strong cytotoxic effect that could inhibit cell survival of HL60 and K562 in a concentration-dependent manner with an $IC_{50}$ of 1.92 and 1.51 μM, respectively. According to Chao et al., cancer cells exposed to tomatine led to a loss of the mitochondrial membrane potential and triggered the release of the apoptosis-inducing factor (AIF) from the mitochondria into the nucleus and downregulated surviving expression [85]. In addition, Rudolf and Rudolf [86] also noted the cytotoxic effect of tomatine on human colon cancer cells was related to lysosomal membrane permeabilization including mitochondrial perturbation with subsequent mitochondrial release of apoptosis-inducing factor (AIF) that contributed to the execution of diverse death phenotypes, possibly via enhanced activity of JNK but in the absence of significant oxidative stress. In another recent study, the effect of tomatine separately and in combination with curcumin on the growth and apoptosis of human prostate cancer PC-3 cell was investigated [87]. In this study, authors reported that a low concentration of both anticancer agents did not have any impact separately, while the combination of these anticancer agents (1 μM tomatine and 5 μM curcumin) synergistically inhibited the growth of cultured prostate cancer cells, mainly associated with inhibition of NF-κB activation and decreased levels of Bcl-2, phospho-Akt, and phospho-ERK1/2. The hydrolysates such as β1 tomatine, γ-tomatine, δ-tomatine, and their common aglycone are reported to have lower activity on the cancer cells than α-tomatine [80, 88].

Like other steroidal GAs, solamargine has been reported to inhibit the growth of human cancer cells, for example, colon (HT-29 and HCT-15), prostate (LNCaP and PC-3), breast (T47D and MDA-MB-231), human hepatoma (PLC/PRF/5), and JTC-26 cells [89, 90]. However, the molecular mechanisms underlying the effect of solamargine to inhibit the growth and induce apoptosis of various cancer cells are poorly understood. Solamargine inhibits proliferation and induces apoptosis in lung cancer cells through p38 MAPK-mediated suppression of phosphorylation and protein expression of Stat3, followed by inducing Stat3 downstream effector p21 [90]. Another study showed that solamargine inhibits the growth of human lung cancer cells through reduction of EP4 protein expression, followed by increasing ERK1/2 phosphorylation [91]. Shiu et al. demonstrated solamargine had a greater cytotoxic effect than cisplatin, methotrexate, 5-fluorouracil, epirubicin, and cyclophosphamide against human breast cancer cell lines. In this study, the authors demonstrated that solamargine upregulated the expressions of external death receptors, such as tumor necrosis factor receptor I (TNFR-I), Fas receptor (Fas), TNFR-I-associated death domain (TRADD), and Fas-associated death domain (FADD). Solamargine also enhanced the intrinsic ratio of Bax to Bcl-2 by upregulating Bax and downregulating Bcl-2 and Bcl-xL expressions. Ultimately, the effects, induced by solamargine, released mitochondrial cytochrome c and activation of caspase-8, -9, and -3 in the cells, indicating that solamargine triggered extrinsic and intrinsic apoptotic pathways to breast cancer cells [92]. Furthermore, no cell cycle arrest was observed in the human myelogenous leukemia K562 cell line, but cytotoxicity to different human cancer cell lines was reported. Solamargine caused membrane disruption and blebbing independent of calcium, and a decrease in ATP

levels. These changes are typical in oncosis, the process leading to necrotic cell death [93–95]. The carbohydrate moiety of solamargine significantly affects its anticancer activity. Considering the difference of the -L-rhamnopyranosyl-(12) between solamargine and khasianine (**Figure 6**), Chang et al. found that the cell death by apoptosis between these two was significantly different. The $IC_{50}$ (dose that inhibits cell growth by 50%) of solamargine, solasodine, and khasianine were 3.0, 2.7, and greater than 20 g/ml, respectively [96].

Furthermore, anticancer properties of solasodine in a mice model were investigated in vivo and it was shown that solasodine glycoside treatments exerted significant inhibition of murine sarcoma 180 cell lines (S180) [97]. Based on further molecular investigation, the probable role of rhamnose in solasodine glycosides binding on tumor cells and its specificity was proposed. About 0.005% mixture of solasodine glycosides (Zycure) was demonstrated to be an effective dose on human beings. About 0.005% exhibited 66 and 78% curability at 56 days and 1 year follow-up, respectively [98]. The possibility of using these GAs from the same and/or different food sources and with other therapeutic agents additively or synergistically has also been taken under consideration. According to Roddick and Rijnenberg, synergism between solanine and chaconine in relation to their membrane-lytic action appeared to be a real and potentially important phenomenon. The two major potato GAs had a significantly greater effect on phosphatidylcholine/cholesterol liposomes at pH 7.2 when used in combination as compared to separately. The latter imparted little or no effect at concentrations up to 1 mM but the former caused greater membrane disruption and leakage of entrapped content at about 100 μM or less [99]. The maximum synergistic effect on C6 rat glioma cells was observed at a ratio 1:1 between α-solanine and α-chaconine at micromolar concentrations [100]. Friedman et al. demonstrated inhibition of liver and stomach cancer cell growth after treatment with α-solanine or α-chaconine alone or in combination. The combination of these two compounds exerted a synergistic, additive, or antagonistic effect on the investigated cell lines [73]. On the other hand, evidence showed that solamargine can be used in combination with some cancer drugs including methotrexate, 5-florouracil, cisplatin, and epirubicin to improve effectiveness on several cancer cell lines and may have potential in breast and lung cancer therapies [92, 101–103]. Furthermore, studies suggest that the combinations of lycopene and α-tomatine, both in pure form and in red and in green tomatoes and tomato products, can have health-improving benefits at lower concentrations than of each bioactive compound alone. Studies suggest that both lycopene and α-tomatine might contribute to the prevention and therapy for human cancers and possibly also cardiovascular diseases [27].

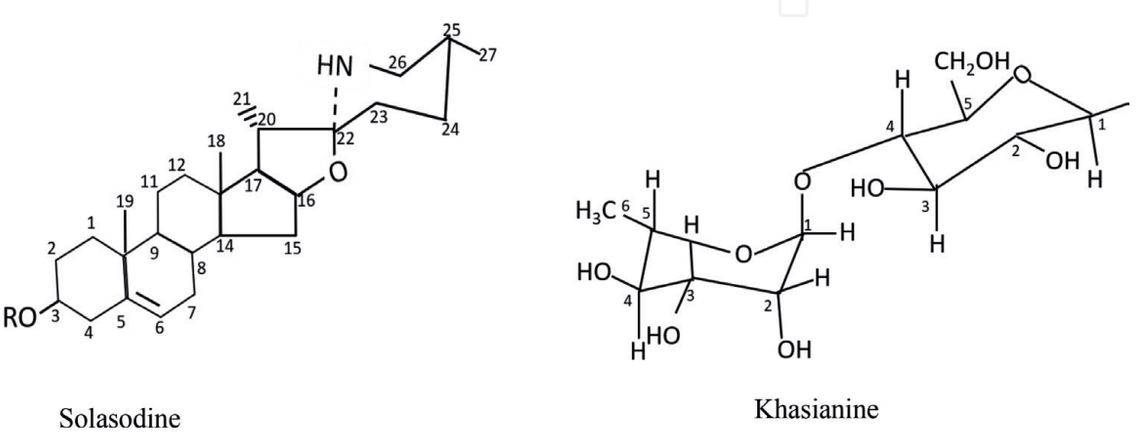



**Figure 6.**
*Structure of solasodine and khasianine (taken from [96]).*

## 6. Antifungal, antimicrobial, and insecticidal activity

In plants, GAs have antimicrobial, insecticidal, and fungicidal properties which account for their protective activity against several insect, pests, and herbivores. α-Chaconine and α-solanine and various *Solanum* sp. extracts have been shown to be toxic to leaf-eating insects, pests of stored products (e.g., seed and flour), mosquitos that feed on animal tissues, termites and cockroaches that feed on feces and garbage, and predatory species [104]. In a recent study, Friedman et al. reported that the GAs α-chaconine and α-solanine were highly active against three pathogenic strains of trichomonads. These authors also reported that the activity of α-solanine was several times higher than α-chaconine; which is contrary to the several previous results where the influence of α-chaconine was reported higher than that of α-solanine [105]. Several other research works regarding the impact of potato glycoalkaloids on the membrane of frog embryos [106–108] and on fungi such as *A. crenulatus*, *A. brassicicola*, *P. medicaginis*, and *R. solani* [109, 110] showed that α-chaconine was more active than α-solanine. Therefore, it appears that the configuration and/or content of the sugar moieties of the molecules influence activity. It has also been reported that the synergism of the two major GAs significantly delivers greater membrane-disruptive activity than either alone. As for example, Fewell and Roddick observed that administration of solanine alone resulted in a minor inhibition in *A. brassicicola* and *P. medicaginis* spore germination; however, significant enhancement in inhibition was observed upon coadministration with α-chaconine [111]. On the other hand, Dahlin et al. showed that α-solanine and α-chaconine exert no significant direct inhibition of mycelial growth of *P. infestans*, while the nonglycosylated unit solanidine has a strong inhibitory effect [112]. It has been reported that the impact of glycoalkaloids on fungi depends not only on the GA structure but also on the species, culture conditions, and development stages of the fungus [111]. Some published reports have indicated the possible use of crude potato extract as an insecticidal source. For instance, Nenaah reported that both potato extract and GAs exhibited considerable acute and residual toxicity against adults of the red flour beetle *Tribolium castaneum* Herbst and the rice weevil *Sitophilus oryzae* L. in a dose-depending manner, but potato extract was more toxic than pure GAs [113]. Moreover, the bactericidal effect of freeze-dried potato peel extract was investigated for mutagenic activity using *in vitro Salmonella typhimurium-Escherichia coli* microsome assay by Stillo et al. These authors, however, proposed that the impact was only significant when used at a higher concentration (100,000 g/ml) [114]. The antibacterial properties of potato peel extract also vary with the species of microorganism examined. For example, Amanpour et al. reported that an ethanol extract from the peel of *Solanum tuberosum* had an antibacterial effect on a spectrum of Gram-positive bacteria, particularly on *S. aureus* but was only effective on one Gram-negative bacteria namely *P. aeruginosa* [115].

Tomato GAs also protect plants against insects and fungal plant pathogens and act by disrupting cell membranes by lysing liposomes [71]. Previously, Roddick [53] reported that a tomatine concentration of 10–30 mg/kg was high enough to be toxic to several fungal species. α-Tomatine has been shown to kill a broad range of fungi and functions as a resistant substance against phytopathogens in the tomato plant [116]. Sandrock and VanEtten examined the impact of α-tomatine on 23 fungal strains and found that both saprophytes and all five pathogens which are nontoxic to tomato were highly sensitive, while all but two tomato pathogens (*Stemphylium solani* and *Verticillium dahliae*) were tolerant to this toxic compound (50% effective dose >300 μM). These authors also tested the sensitivity of the fungal isolates to the hydrolysis products of α-tomatine (β2 tomatine and tomatidine) and found them to be less toxic to most pathogens but inhibitory to some

of the saprophytes and nonpathogens of tomato [116]. According to several other published results, the hydrolysis products of tomatines possess reduced antifungal activity [43, 117]. In fact, it has been previously reported that fungal tomato pests such as *Septoria lycopersici* and *Fusarium oxysporum* have been found to produce extracellular enzymes that hydrolyze glycosidic bonds within the saccharide chain of α-tomatine, which not only exhibit reduced antifungal activity but also cause suppression of induced plant defense mechanisms such as hypersensitive responses and oxidative burst [117, 118]. Furthermore, a preliminary screening showed that tomatine at a concentration of 100 μM completely inhibited the growth of the *Trichomonas vaginalis* strain G3, *Tritrichomonas foetus* strain D1, and *Tritrichomonas foetus* strain C1, while much less inhibition was found in the case of tomatidine [119]. However, in contrast, Simons et al. found that the aglycone tomatidine has far more antifungal activity toward yeast and a more distinct mode of action than α-tomatine [120]. The membrane lytic effect of α-tomatine is pH dependent, and it has also mentioned that some fungi are able to colonize α-tomatine-containing tomato tissue by lowering the pH of the infection site [121].

Like other steroidal GAs, there is also some evidence that solasonine and solamargine possess antifungal, insecticidal, and molluscicidal activities. Both glycoalkaloids are reported to inhibit growth of the spiny bollworm, lettuce seedlings, and molluscs, while solasonine is weakly antiviral [122–126]. The antifungal activity has also been reported for solamargine and to a lesser extent for its aglycone solasodine [127, 128]. Furthermore, inhibition of red flour beetle larvae, tobacco hornworms, and *Trypanosoma cruzi* by solamargine has been reported [128, 129].

## 7. Other biological activities

In addition to the activities reported above, some GAs have been reported to possess antibiotic, antiallergenic, antipyretic, anti-inflammatory, and anti-hyperglycemic activities at certain doses and conditions. Choi and Koo studied the analgesic and anti-inflammatory effect of a potato extract. They reported that an ethanolic extract of potato resulted in a significant effect in three types of pain induction suggesting that its analgesic effect may in part be related to its anti-inflammatory neurogenic and narcotic properties [130]. The antinociceptive effect of the potato extract may be related to the reduction in $Ca^{2+}$ influx at the axon terminal of the afferent nerve inducing a decrease in adenylyl cyclase activity, which results in decreased levels of cyclic AMP and efflux of $K^{+}$ ions. The latter lead to hyperpolarization of the nerve and finally an apparent antinociceptive effect [131]. A recent study highlighted a significant reduction in the production of both proinflammatory cytokines (interleukin-2 and interleukin-8) with sublethal concentrations of α-chaconine (~22% reduction in production of both cytokines) and solanidine (~35% reduction in production of both cytokines) [132]. Shin et al. reported that α-solanine had potential therapeutic value for treatment of inflammatory diseases. The anti-inflammatory effect of solanine was reported to be mediated via the regulation of proinflammatory cytokines in an LPS-induced systemic inflammation mouse model and in RAW 264.7 macrophages [133]. Similarly, tomatine imparted an anti-inflammatory effect to the rats [134]. Although the anti-inflammatory mechanism of α-tomatine is not well understood, results showed that α-tomatine significantly suppressed the production of proinflammatory cytokines in lipopolysaccharide-induced macrophages. Moreover, lipopolysaccharide-mediated nuclear translocation of the nuclear factor-kappa B (NF-κB)-p65 and phosphorylation of extracellular signal-regulated kinase (ERK) 1/2 were attenuated after α-tomatine treatment [135]. In addition, tomatidine exhibited more active

anti-inflammatory activity and less toxicity than solasodine. The anti-inflammatory activity of tomatidine is proposed to be due to blocking NF-kB and JNK signaling [136]. The antimalarial activity of chaconine has been reported by Chen et al. Chaconine showed a dose-dependent suppression of malaria infection; at a dose of 7.50 mg/kg, the parasitemia suppressions of chaconine, tomatine, solamargine, solasonine, and solanine were 71.38, 65.25, 64.89, 57.47, and 41.30%, respectively [137]. Furthermore, solanine injected to normal rats increased the blood sugar level, while decreasing of sugar level was observed in case of adrenalectomized rats [138]. Hyperglycemia appears to be due to stimulation of the adrenal gland by solanine. The latter was accompanied by a decrease in glycogen levels in the livers [14]. Another study reported that feeding unripe tomato to the rats significantly reduced blood glucose level compared to the ripe tomatoes, probably due to the presence of large of amount of glycoalkaloids such as tomatine, dehydrotomatine, and tomatidine [139]. On the other hand, it has been reported that a green tomato-rich diet can contribute to cholesterol reduction due to the formation of a complex between α-tomatine and cholesterol [51].

## 8. Conclusion

In this chapter, information on the distribution of steroidal GAs in the plants of *Solanaceous* family, their harmful effects as well as the beneficial aspects have been reviewed and discussed. GAs are naturally occurring agents which serve a plant protective role in many important commonly consumed plants. Due to their dose-dependent toxicity, excessive accumulation during growth, harvesting, and postharvest practices could lead to the human health problems. On the other hand, if extracted from source, these GAs could be beneficially utilized as insecticide, antimicrobial, and antifungal agents. In recent years, anticancer activity of these compounds has been studied intensively. However, to establish these GAs in cancer treatment, more research works are needed to understand its mechanism and the harmful effects on the normal living cells. In addition, better strategies for recovery of these agents from their natural sources which take account of the need for sustainability need to be further developed. A better understanding of the role of GAs in the plant is also essential to exploit their benefits more effectively by clearly understanding their biological properties which recognizes not only the complexity of living cells, but also the capacity for unique interrelationships between some or all the component compounds.

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