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Molecules of Interest

# Solanesol: Added value from *Solanaceous* waste

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ABSTRACT

Isoprenoids, also known as terpenoids, are the largest and oldest class of natural products known. They are comprised of more than 40,000 different molecules all biosynthetically related via a common five carbon building block (isopentenyl). Many isoprenoids are of commercial interest and are used as fragrances in cosmetics and flavours, colorants and nutritional supplements in foods and feeds as well as being phytomedicines. Their industrial relevance also means they are compounds of high value with global markets in the range of $1 billion per annum. Solanesol is a 45-carbon, unsaturated, all-*trans*-nonaprenol isoprenoid of high value. Recently this molecule has received particular attention because of its utility, both in its own right and as a precursor in the production of numerous compounds used in the treatment of disease states. Instability in supply and spiralling costs have also lead to the search for sources. In this article existing sources and the potential strategies and tools available to create sustainable biosources are reviewed.



## 1. The occurrence of solanesol

In recent years, it has become apparent that even in commonly cultivated crop species, there are significant levels of medicinal compounds that could form the basis of therapies. One example comes from the isoprenoid family of metabolites, also known as terpenoids representing the largest and oldest class of natural products known, consisting of more than 40,000 different molecules (Withers and Keasling, 2007).

Solanesol is a 45-carbon, all-trans-nonaprenol, first isolated from flue-cured tobacco. The content of solanesol in tobacco has been the subject of several studies (for example, Zhao et al., 2005; Zhou and Liu, 2006). In tobacco leaf samples from 16 regions of China, solanesol content ranged from 0.4% to 1.7% dry weight (Zhou and Liu, 2006), indicating a strong influence of environment and/or genetic background. Although Zhou and Liu (2006), demonstrated that leaves accumulated ca. 4-fold greater levels of solanesol than in stems, their study was confined to a single cultivar. Another study (Kotipalli et al., 2008) considered several tobacco cultivars and showed that leaf solanesol content ranged from mean values of 0.05% dry weight to 1.77%. The reason for this variation is not clear although it is known that in general solanesol content increases with leaf age (Hemming, 1985). Solanesol is also present in other plants from the *Solanaceae* including tomato, potato, eggplant and pepper (Kotipalli et al., 2008). A detailed survey of levels of solanesol in these species is lacking although values for unspecified cultivars have been published (Kotipalli et al., 2007, Table 1). As with tobacco, there is considerable variation in the levels of solanesol found in potato foliage, ranging from 1.5% of dry weight (Asahina et al., 1977) to 0.04% per gram fresh weight (Ma et al., 2009). In species outside the *Solanaceae* there is even less information about solanesol accumulation. Reports indicate that solanesol can be detected in leaf extracts of soybean (Kurisaki et al., 1996) and spinach (Sakaihara et al., 2000) although quantitative data has not been published. Clearly there is a requirement for more detailed insights into the organs and tissues in which solanesol accumulates, the variation in levels between germplasm and the developmental stage or the optimal environmental conditions under which solanesol is synthesised. However, already it is recognised that by-products of crop products may be utilised for the extraction of solanesol. One example is the use of tobacco waste (Machado et al., 2010) however it is worth considering other sources, especially with the greater investments in biorefining. Obvious examples include potato and tomato foliage. Potato and tomato are the most common fruit and vegetables produced worldwide. Total production in 2006 was up to 350 Mtonnes, of which 40% was produced in Europe (www.faostat.fao.org). During the processing of tomato and potato products up to 40% of the initial material entering the plant ends up as waste. In addition to the fruit or tuber material, after harvest vegetative material must be disposed of. Typically potato produces 4 tonnes per hectare dry weight of foliage (Carruthers and Pirie, 1975). In general, vegetative waste material is treated chemically to stop the spread of disease prior to undergoing pulping, composting or incineration. Harsh chemical treatments including the application of alkalis or

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**Table 1**
Solanesol content in plant tissues.

| Species | Tissue | Solanesol content (% dry weight) | Reference |
|---|---|---|---|
| *Nicotiana tabacum* | Leaf | 0.64–0.57 | Zhao et al. (2005) |
| | Stalk | 0.19–0.06 | Zhao et al. (2005) |
| | Flower | 0.03 | Zhao et al. (2005) |
| *Nicotiana tabacum* | Leaf | 0.40–1.70 | Zhou and Liu (2006) |
| *Nicotiana tabacum* | Leaf | 0.05 – 1.77 | Kotipalli et al. (2008) |
| *Solanum tuberosum* | Leaf | 1.0–3.0 | Asahina et al. (1977) |
| *Solanum tuberosum* | Leaf | 0.40 | Kotipalli et al. (2008) |
| *Solanum tuberosum* | Leaf | 0.04 | Ma et al. (2009) |
| *Solanum melonga* | Leaf | 0.40 | Kotipalli et al. (2008) |
| *Solanum lycopersicum* | Leaf | 0.35 | Kotipalli et al. (2008) |
| *Capsicum annum* | Leaf | 0.35 | Kotipalli et al. (2008) |
| *Datura stramonium* | Leaf | 0.15 | Kotipalli et al. (2008) |
| *Solanum nigrum* | Leaf | 0.25 | Kotipalli et al. (2008) |
| *Nicandra physaloides* | Leaf | 0.30 | Kotipalli et al. (2008) |
| *Cestrum nocturnum* | Leaf | 0.05 | Kotipalli et al. (2008) |
| *Solanum xanthocarpum* | Leaf | 0.25 | Kotipalli et al. (2008) |
| *Glycine max* | Leaf | Not specified | Kurisaki et al. (1996) |
| *Spinacea oleracea* | Leaf | Not specified | Sakaihara et al. (2000) |

acids such as sulphuric acid are presently used. However, new legislation will soon be in place to prevent these practices. To date there has been very little work performed to utilise this substantial biomass for co-product isolation but the potential for using this material for solanesol extraction should be explored.

## 2. Biosynthesis

The formation of isoprenoids such as solanesol is a complex process that is compartmentalised and under developmental regulation (reviewed in Logan et al., 2000). All isoprenoids are composed of isoprene units derived from the common pre-cursor isopentenyl diphosphate (IPP). Since the discovery of the mevalonic (MVA) pathway in the 1950s it was assumed that IPP was synthesised from acetyl-CoA via mevalonic acid (MVA) (Goldstein and Brown, 1990). However experimental data consistently indicated that the MVA pathway could not account exclusively for the formation of plastid-derived isoprenoids (Lichtenthaler et al., 1997; Phillips et al., 2008). In the early 1990s retro-biosynthetic labelling conclusively established the presence of an alternative, MVA-independent pathway for the formation of IPP and dimethylallyl diphosphate (DMAPP). The utilisation of functional genomics has now elucidated the biosynthetic steps responsible for the MVA-independent pathway in plants and bacteria. A key feature of this pathway is its plastid localisation. Thus it is now clear that two pathways for IPP formation exist and are separately localised in plastid and cytosol. These pathways are not mutually exclusive and labelling studies and analysis of transgenic plants have indicated that under certain conditions and at some stages of plant development transfer of metabolites between the two pathways can arise (reviewed in Bouvier et al., 2005). Fig. 1 provides an overview of isoprenoid biosynthesis in plants including the subcellular location of the two IPP forming pathways. Feeding experiments were independently performed with [1-$^{13}$C]deoxy-D-xylulose triacetate and (RS)-[2-$^{13}$C]mevalonolactone in tobacco plants (Fukusaki et al., 2004). From the labelling pattern of solanesol it was concluded that the isoprene moiety of solanesol was derived from deoxy-xylulose. The result strongly suggests that tobacco solanesol is biosynthesised via the MVA-independent pathway locating its synthesis to the plastid.

Prenyl phosphates represent the central backbone of the isoprenoid pathway from which all isoprenoid sub-groups are derived. The five carbon substrates used are IPP and DMAPP. These molecules lead to the formation of longer chain prenyl lipids such as GPP ($C_{10}$), FPP ($C_{15}$), GGPP ($C_{20}$), octaprenyl diphosphate ($C_{40}$) and solanesyl diphosphate ($C_{45}$). *Arabidopsis* genes involved in isoprenoid metabolic networks were reviewed in detail by Lange and Ghassemian (2003). In solanesol diphosphate biosynthesis sequential condensation of farnesyl diphosphate with isopentenyl diphospate occurs until the $C_{45}$ chain length is achieved. The condensation reactions are catalysed by a trans-prenyltransferase enzyme (TPT, synonym solanesol diphosphate synthase). In *Arabidopsis* it was predicted that the genome contained two *TPT* encoding genes (Lange and Ghassemian, 2003) and these (SPS1 and SPS2) have been functionally characterised (Hirooka et al., 2003; Jun et al., 2004). Solanesyl diphosphate, is a crucial biosynthetic precursor of important quinone compounds, such as ubiquinone in mitochondria and plastoquinone in plastids (Swiezewska and Danikiewicz, 2005, Fig. 1).

Whereas SPS1 was localised in the endoplasmic reticulum (ER), SPS2 localised to the plastid. As it is well known plastoquinone biosynthesis occurs in the plastid, this observation implies that SPS2 is involved in plastoquinone biosynthesis. However the ER localisation of SPS1 is more difficult to explain as ubiquinone is considered to be synthesised in the mitochondria based on the observation that *Arabidopsis* Ppt1, which catalyses the first step of ubiquinone synthesis is localised in the mitochondria (Okada et al., 2004). In spinach, prenyl diphosphate synthase is localised in the endoplasmic reticulum (Swiezewska et al., 1993), which is consistent with the SPS1 localisation and suggests the synthesis of the polyprenyl moiety of ubiquinone is synthesized in the ER, prior to transfer to the mitochondria.

More recently, two *SPS* genes from rice have been characterised (Ohara et al., 2010). In this case the OsSPS1 protein localised to the mitochondria whereas OsSPS2 localised to the plastid, suggestive of their involvement in ubiquinone and plastoquinone biosynthesis, respectively. The substrate specificity of OsSPS1 and OsSPS2 were also investigated and it was shown that the preferred substrate for OsSPS1 was FPP whereas for OsSPS2, it was GPP. In tobacco, transplastomic over-expression of *1-deoxy-D-xylulose reductoisomerase* (*DXR*) which catalyses the first committed step of plastidial isoprenoid-precursor biosynthesis, resulted in significant increases in the accumulation of many isoprenoids including solanesol (Hasunuma et al., 2008). Although this result demonstrates that solanesol is synthesised in the plastid, it does not exclude the possibility that solanesol is also synthesised in other cellular localisations and given the ER localisation of the *SPS1*-specific transcript in spinach and *Arabidopsis*, this possibility remains open.

Biosynthetically, solanesol is derived from solanesyl diphosphate (SPP) and occurs in both free and esterified forms (Rowland and Latimer, 1959). Solanesyl ester fractions from tobacco yield a series of fatty acids and solanesol when hydrolysed (Scholtzhauer et al., 1976). Rowland and Latimer (1959) found that solanesol combined with palmitic, linoleic, linolenic, myristic and oleic acids and two unidentified acids. It was also reported that solanesol

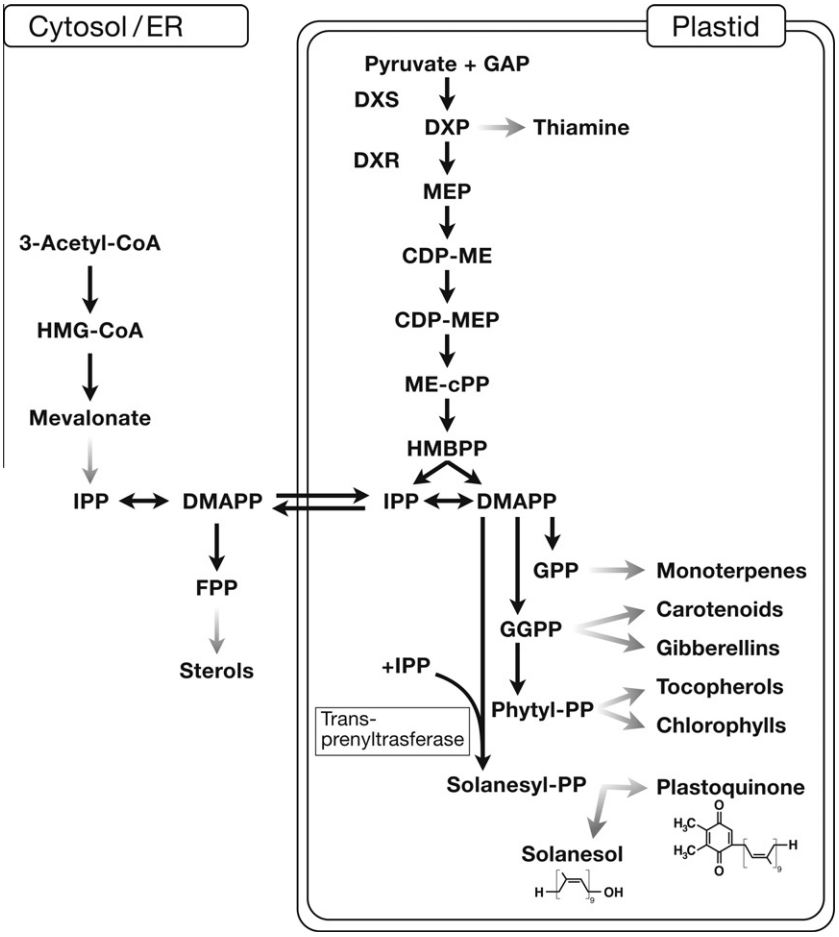


**Fig. 1.** Solanesol biosynthetic pathway in higher plants. GAP, glyceraldehyde-3-phosphate; DXP, 1-deoxy-D-xylulose-5-phosphate; MEP, 2-C-methyl-D-erythritol-4-phosphate; CDP-ME, 4-diphosphocytidyl-2-C-methyl-D-erythritol; CDP-MEP, 4-diphosphocytidyl-2-C-methyl-D-erythritol-2-phosphate; ME-cPP, C-methyl-D-erythritol-2,4-diphosphate; HMBPP, hydroxymethylbutenyl-4-diphosphate; IPP, isopentenyldiphosphate; DMAPP, dimethylallyl diphosphate; GPP, geranyl diphosphate; FPP, farnesyl diphosphate; GGPP, geranylgeranyl diphosphate; Phytyl-PP, phytyl diphosphate; HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA.

occurs as the acetate, octanoate, decanoate and in combination with phytosterols such as stigmasterol and β-sitosterol (Stedman, 1968) The conversion of SPP to solanesol/solanesol esters requires further investigation in order to identify whether there are specific phosphorylases and acyltransferases in the conversion of SPP to free solanesol/solanesol esters. If attempts are to be made to use plants as green factories for the production of solanesol, the form in which solanesol accumulates and the storage mechanisms could be critical. Genetic and molecular biology tools in concert with analytical platforms have recently been developed for many of the *Solanaceae*, particularly potato (http://potatogenomics.plantbiology.msu.edu/) and tomato (http://solgenomics.net/) and it is timely to investigate such processes.

No definitive biological functions have been ascribed to free polyisoprenoid alcohols or their carboxylic esters, the main accumulated forms, although recent work has made some progress in this respect (Bajda et al., 2009). In tobacco leaves infection with tobacco mosaic virus (TMV) resulted in an increase of up to 7-fold in the level of solanesol and significant increases in the levels of other polyprenol alcohols only in a resistant cultivar (*Nicotiana tabacum* cv. Samsun *NN*). In susceptible cultivars no significant increase was measured. Hydrogen peroxide also elicited a significant increase in solanesol content, leading to the suggestion that polyisoprenoid alcohols may have a role in protection against reactive oxygen. Irrespective of the role of solanesol in the plant, little is known about the regulation of solanesol accumulation in plant tissues. Further work is required to characterise the solanesol biosynthetic pathway, and explore the limits to which solanesol can accumulate. The site of accumulation and form in which solanesol accumulates are also topics worthy of further investigation if a metabolic engineering approach is to be used to optimise production.

## 3. Uses of solanesol

Solanesol in its own right has useful medicinal properties and is known to possess anti-bacterial, anti-inflammation, and anti-ulcer activities (Serebryakov and Nigmatov, 1990; Khidyrova and Shakhidoyatov, 2002). Furthermore, other solanesol conjugates such as *N*-solanesyl-*N,N′*-bis (3,4-dimethoxybenzyl) ethylenediamine (SDB) and its derivatives (Wang et al., 2007) have received significant attention with respect to their ability to reverse multidrug resistance and sensitise tumour cells to conventional anticancer treatments. For example Taxol™-resistance in bladder cancers has been a recent target, whereby the use of solanesol'' derivatives can reverse resistance to Taxol™ (Enokida et al., 2002; Sidorova et al., 2002).

Industrially, solanesol is used by the pharmaceutical industry as an intermediate in the synthesis (both chemically and biotechnologically) of metabolically active quinones such as coenzyme Q10 and vitamin K analogues (Naruta, 1980; Hamamura et al., 2002; Choi et al., 2005). The demand for solanesol continues to escalate

since coenzyme Q10 entered the market as a dietary supplement (Lipshutz et al., 2005) largely due to its perceived benefits in providing relief for migraine headache sufferers (Sándor et al., 2005), protecting people from Parkinson's disease and other neurodegenerative diseases (Matthews et al., 1998; Shults et al., 2002, 2004; Müller et al., 2003), and improving blood pressure and long-term glycaemic control for patients with type 2 diabetes (Hodgson et al., 2002).

Coenzyme Q10 has a "head" and "tail" structure, comprised of a quinone-derived head and an isoprenoid tail. It can be produced by chemical synthesis (Negishi et al., 2002), semi-chemical synthesis from solanesol (Lipshutz et al. 2005) and microbial fermentation using a range of genera including *Agrobacterium*, *Rhodobacter* and *Paracoccus* (Yoshida et al., 1998). The biosynthesis of coenzyme Q10 by prokaryotes has been described in detail (reviewed in Choi et al., 2005; Corinne et al., 2007). Coenzyme Q10 produced by fermentation is considered the most viable approach because of the ability to produce biologically potent coenzyme Q10 without optical isomers and at reduced costs (Corinne et al., 2007; Choi et al., 2005). Supplementing bacterial fermentations with leaf hydrolysylates rich in solanesol was demonstrated to enhance the yield of coenzymeQ10 by up to 100% (Tian et al., 2010). However the semi-synthetic method of Lipshutz et al., 2005, is also an efficient means of production. In this process a chloromethylated coenzymeQ moiety derived from gallic acid, enables the direct formation of CoQ10 via nickel-catalysed cross-coupling with the solanesol-derived side chain in the form of an *in situ*-derived vinyl alane (Fig. 2). This process results in the formation of all-trans coenzyme Q10.

## 4. Purification

Purification of solanesol has focussed on using tobacco leaves as the starting material. Many protocols have been published, including conventional heat reflux extraction (Keca et al., 1997), solid phase extraction (Tang et al., 2007), ultrasound- (Keca et al., 1997; Chen et al., 2007), microwave-assisted extraction (Zhou and Liu, 2006), counter-current chromatography (Zhao and Du, 2007; Rao et al., 2008) and supercritical fluid extraction (Ruiz-Rodriguez et al., 2008). The curing process has been shown to enhance the release of bound solanesol in the form of esters from flue-cured tobacco products (Severson et al., 1977; Chamberlain et al., 1988; Liu et al., 1998) and wastes (Zhao et al., 2005; Qiu et al., 2007). Several of these approaches have been used for the commercial production of solanesol, predominantly in China. Recently, approaches for the extraction of solanesol as a co-product of tobacco protein production has been systematically examined in an attempt to find economically viable alternative uses for tobacco (Machado et al., 2010). Purification of solanesol from other members of the *Solanaceae* such as potato has received much less attention although there are some reports of extraction from potato foliage (Ma et al., 2009).

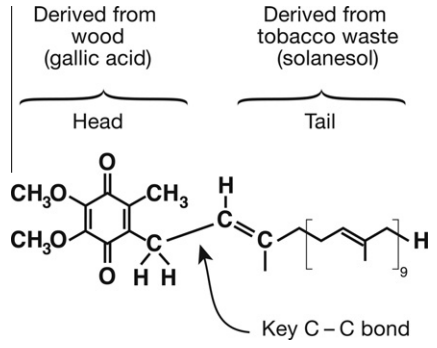


**Fig. 2.** The structure of coenzyme Q10 indicating the origins of the "head" and "tail" portions of the molecule.

## 5. Prospects for further research

There are many exciting possibilities for uses of solanesol, both as a precursor of co-enzyme Q10 and as a therapeutic agent in its own right. Its presence as a co-product in the crops such as tobacco, potato and tomato raises interesting economic possibilities for adding value to the crop, however there are gaps in our knowledge regarding the genetics and environmental factors that impact on accumulation levels. Further work is required in these areas as is a full assessment of natural variation and in metabolic engineering approaches to enhance solanesol level.

In conclusion further work is required to; (i) fully assess the natural variation that exists in solanesol content, (ii) determine the environmental factors that impact on yields, (iii) develop tools and strategies for metabolic engineering and (iv) develop environmentally friendly extraction processes. A greater insight into these areas will hopefully lead to the development of economically sustainable biosources of solanesol with low environmental impact.

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