Reasons for opposition against European Patent EP 1 515 600 B1

Title: FLAVONOL EXPRESSING DOMESTICATED TOMATO AND METHOD OF PRODUCTION
Application number: 03760244.8
Proprietor: Syngenta Participations AG, 4058 Basel (CH)
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Reasons for opposition:

(1) Art 53 a – morality and ordre public

The patent must be considered to be bio-piracy, since it is based on the misappropriation of biodiversity:
The plant characteristics as claimed in the patent are derived from tomatoes (so called accessions) that stem from the countries of origin in Latin America.

In more detail, the plants were derived via the University of California (see Willitis, et al., 2005). But originally they stem from Peru (accession LA1926, *L. pennellii v. puberulum*, see http://tgrc.ucdavis.edu/Data/Acc/AccDetail.aspx?AccessionNum=LA1926) and Chile (LA1963 and LA2884, both *L. chilense*, see http://tgrc.ucdavis.edu/Data/Acc/AccDetail.aspx?AccessionNum=LA1963 and http://tgrc.ucdavis.edu/Data/Acc/AccDetail.aspx?AccessionNum=LA2884). In its patent, Syngenta does not mention the original sources, and no indication is given of whether the original plants were received lawfully and in accordance with the Convention on Biodiversity, the Nagoya Protocol, and with the consent with the local communities.

Since the invention is based on biodiversity found in the countries of origin and the plant characteristics as described, the patent is a misappropriation of the genetic resources: All crosses between the accessions and commercial varieties to raise the level of flavonols in tomato plants are claimed as an invention. Therefore, the patent is considered to be bio-piracy, and as such in conflict with Art 53 of the EPC.

(2.1) Art 53b – plant varieties

The patent extends to all plant varieties showing the plant characteristics as described. Thus, the granting of this patent violates the prohibition on granting patents on plant varieties under Article 53b.

The current decision-making of the EPO regarding the patentability of plant varieties is based on decision G1/98 and Rule 27 b. If these are applied to the patent opposed, the patent has to be revoked for the following reasons: In G1/98, plant varieties with characteristics that are based on a genotype (a specific combination of genetic conditions) are regarded as not patentable. However, plant characteristics that are defined by a single DNA sequence and can be transferred to other plants by technical means, are regarded as being patentable. For example, a genetically engineered plant which has had a gene inserted into its genome in order to make it herbicide-resistant would not be a plant variety as such plant grouping would not be defined by its whole genome, but by a characteristic linked to a specific defined and inserted DNA i.e. the herbicide resistance.

But the characteristics as claimed in claim 1 (higher level of flavonols in the peel and the flesh of the fruits) are the result of a combination of genotypes and not related to a distinct part of DNA. Thus, the characteristics of these plants have to be more accurately described as stemming from “a given genotype”, but not as being “defined by single DNA sequence”. This observation is based on several facts and findings:

(1) The paper published by the inventors in 2005 (Willitis et al., 2005) states that the tomatoes used for crossing did not show the claimed characteristics i.e. a higher level of flavonols. They only showed the desired qualities after crossing, in combination / interaction with other genetic elements that were not present or inactive in the parental plants. Only after crossing the plants (*L. pennellii v. puberulum*) with varieties of *L. esculentum*, did the resulting plants show the desired content of flavonols. Thus, Willitis et al (2005) conclude that not only the CHI gene and its activity in the flesh of the tomato (which Syngenta used for the selection of the accessions), but other, so far not identified genetic conditions have to be met to produce plants with a higher level of flavonols in peel and flesh:

> “The most promising accession, *L. pennellii v. puberulum* (LA1926), had high level expression of the pathway genes in the peel and flesh tissue but showed only modest levels of flavonoid accumulation as compared to tomato lines transformed with the CHI gene. This result clearly demonstrates the value of an RNA-based approach to screen potential germplasm, as the flavonoid levels alone will not identify appropriate germplasm for the high flavonoid trait. Although it is not clear why *L. pennellii v. puberulum* accumulates low levels of flavonoids, progeny from the interspecific cross accumulated high levels of flavonoid in the fruit peel and flesh (Figure 5 and Table 2). At least one genetic factor responsible for the lack of CHI expression in the peel appears to be a mutation in a fruit

> specific element of the promoter, whereas induction of the pathway in the flesh certainly involves additional contributing regulatory factors. Further investigation will be necessary to understand the nature of increased gene expression in the flesh tissue."

Thus, one has to assume that the pattern of gene expression depends on the genetic background of the plants and a combination of the genotypes.

(2) This finding is also backed by the fact that tomatoes that were genetically engineered in a such a way that the CHI gene became active in the flesh of the plants showed different characteristics compared to those plants found in the centre of origin (such as LA1926). As explained by Willitis et al. (2005):

> "To date, transgenic high flavonoid tomato lines have been created by overexpressing a heterologous CHI gene (…) flavonoids were produced throughout the fruit, but the induction of tomato genes by the maize transcription factor was apparently not uniform and led to altered patterns of flavonoid accumulation. The breeding approach outlined in this report resulted in more uniform expression of flavonoid pathway genes and high level accumulation of quercetin in both peel and flesh."

Again, one has to assume that the pattern of gene expression depends on the genetic background of the plants and the combination of genotypes.

(3) Eshel and Zamir (1996) describe epistatic effects if *L.esculentum* is crossed with *L. pennelli*. These effects can vary between the different crossings, showing that the genetic background of the tomato plants being used is decisive for many characteristics derived from these crossings. These observations are especially relevant when quantitative trait loci (QTL) are involved in the respective plant characteristics. Since the three accessions used by Syngenta (LA1926, LA 1963 and LA 2884) al show activity of the CHI gene in the flesh, but render different content of flavonols, the characteristics described depend on a quantitative trait locus (QTL) that can vary in degree and can be attributed to polygenic effects.

Again this is a clear indication that the plant characteristics as claimed are based on specific genotype.

(4) A further decisive observation is that the intended high level of flavonols as claimed can

apparently only be achieved if accession LA1926 is used. It can be understood from Willitis et al (2005), that accession LA1926 is different from the other two candidates which also show CHI activity in the flesh (LA1963 and LA 2884): For example, Figure 4 shows that in LA1926, not only Chalcone Isomerase (CHI) but also Chalcone Synthase (CHS) is active in the flesh of the fruit. This is not the case in LA1963 and LA2884. Furthermore, Willitis et al. (2005) very clearly state that there are substantial differences between these accessions in regard to the goal of their plant breeding:

> "The most promising accession, L. pennellii v. puberulum (LA1926), had high level expression of the pathway genes in the peel and flesh tissue (...)"

This observation (which is also relevant in respect to Article 83, see below) underpins that a given genotype or a combination of genotypes is decisive for the plant characteristics as claimed.

Consequently, the patent has to be revoked under Art 53 (b) in connection with Rule 27, EPC.

It should also be taken into account that the criterion "if the technical feasibility of the invention is not confined to a particular plant or animal variety" (Rule 27 b and Article 4. 2 of the EU Directive 98/44) cannot be applied in this context to defend the patent. It has to be assumed that in Directive 98/44 the term "technical feasibility" is only directed at processes for genetic engineering, which enable the transfer of DNA sequences beyond the boundaries of species. There is no doubt that the overall purpose of Directive 98/44 was to allow patents in the area of biotechnology – its title is "Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions". This view is also supported by the wording of the Directive. For example, recitals such as 52 and 53 of Directive 98/44/EC only discuss the compulsory cross-license in the field of exploitation of new plant characteristics resulting from genetic engineering. The wording of Article 4. 2, which is decisive in this context ("*Inventions which concern plants or animals shall be patentable if the technical feasibility of the invention is not confined to a particular plant or animal variety*"), can easily be derived from the technical background of genetic engineering i.e. working with isolated DNA that can be transferred even beyond the limits of species. In this context, the criterion has a specific technical meaning.

But in conventional breeding – as used in this case - we have a different situation. Any plant characteristic can be transmitted to any other variety simply by employing further breeding, but only within the same species. In this regard, it does not matter if the plants are characterised by a single gene or by larger parts of its genome. As a result, the criterion as given in Article 4.2. and applied by the EPO does not have a specific technical meaning and does not provide any legal clarity in the context of conventional breeding.

In summary, if the provisions of Article 53(b) are applied to these plants the patent has to be revoked. Otherwise, the prohibition of patenting plant varieties would become meaningless.

Furthermore, in this context, it should be noted that there is no legal basis for an argument saying that those plants that cannot be protected under the plant variety protection (PVP) system should possibly be protected under patent law. As stated in the EPC, plants that meet the criteria of Rule 26 (4) (a) – (c), EPC, have to be considered as plant varieties *irrespective of whether the conditions for the grant of a plant variety right are fully met*". (EPC, Rule 26 (4)) For example, a "line" of plants that cannot be protected under PVP law can still fall under the exclusion of Article 53(b).

(2.2) Art 53b – essentially biological processes for breeding

In 2015, the Enlarged Board at the EPO finally gave an extremely problematic interpretation of current patent law. While processes for conventional breeding cannot be patented, plants and animals stemming from these processes are patentable (decisions G02/12 and G02/13). However, this decision needs to be reconsidered since it completely undermines the relevant prohibitions in European patent law. Consequently, the prohibition of Article 53b can no longer be applied in a meaningful way. This has also been noted by the EPO. As the Technical Board of Appeal in its interlocutory decision of 31 May 2012 wrote (case T1242/06[1]):

> The board still has to address the further argument that, (…) it would be wrong to the claimed subject-matter to be patented, since this would render the exclusion of essentially biological processes for the production of plants completely ineffective, thereby frustrating the legislative purpose behind the process exclusion in Article 53(b) EPC. (Nr. 40)
>
> Disregarding the process exclusion in the examination of product claims altogether would have the general consequence that for many plant breeding inventions patent applicants and proprietors could easily overcome the process exclusion of Article 53(b) EPC by relying on product claims providing a broad protection which encompasses that which would have been provided by an excluded process claim (...). (Nr. 47)

[1]http://www.epo.org/law-practice/case-law-appeals/pdf/t061242ex2.pdf

According to the reasoning issued by the European Patent Office itself, it does not make sense to exclude just the processes for breeding while allowing patents on plants and animals: It would be too easy to escape the prohibition simply by clever drafting of the claims. And, as mentioned, the prohibition in Article 53b could no longer be applied in a meaningful way.

In the case at issue, the plants are derived from a process of crossing and selection, which has to be considered as being essentially biological. Although these processes are not claimed explicitly, the patent as granted represents a violation of Art 53b since it renders it impossible to apply the respective process for breeding without infringing the patent. Looking at the wording of claim 1, the respective process for breeding is used to describe the product. Usage of the process (if successful) would inevitably lead to the production of plants as claimed.

Upholding the patent would create a situation that is the exact opposite of what the legislators intended. The patent provides the patent holder with a monopoly on all plants with the respective characteristics, the seeds and even the fruits and food derived thereof - which goes much further than a patent on the process would cover.

(3) Art 56 - inventiveness

In general, all experts in this field know that biological diversity in the countries of origin in many cases will overcome the restrictions in plants breeding within commercial varieties of tomatoes, which often suffers from a narrow genetic basis (see Hammond, 2012).

Further, it is well known that lines of wild tomatoes can be crossed with varieties being traded commercially. The processes for crossing the plants are not inventive and Syngenta does not claim inventiveness for these processes.

But, neither is the way in which the plants were selected an inventive step. As several publications show, it was previously commonly known that there are some genetic elements that influence the flavonol in the fruits. As stated by Verhoeyen et al (2002):

> The investigations to date indicate that *chi* gene activity appears to be key to flavonol accumulation in tomato peel, whilst *chs* and *fls* activities are required for the production of favonols in flesh tissue. Therefore, it was reasoned that, to achieve increased flavonol accumulation throughout the tomato fruit, ectopic expression of three genes encoding the

> biosynthetic enzymes CHS, CHI and FLS would be sufficient. Indeed a cross harbouring these three genes accumulates increased levels of quercetin-glycosides in peel and kaempferol-glycosides in flesh (S Colliver, unpublished results). It is also noteworthy that a similar phenotype can be achieved by crossing tomatoes containing Lc and C1 transgenes with tomatoes containing the CHI transgene (S Muir, unpublished results).

Thus, it was simply a logical step devoid of inventiveness to screen for tomatoes with CHI, CHS activity and FLS gene activity in the flesh of the fruit. These are the exact genes and gene products Syngenta was looking for in its "invention" (see Figure 4, Willitis, 2005).

Further, Verhoeyen et al (2002) had already put forward the idea of using crossing and selection to achieve tomato plants with a higher content in flavonol. From the perspective of "inventiveness", it does not make a difference whether transgenic plants or accessions from the country of origin were used by Syngenta.

(4) Art 54 - the products as claimed are not new

The patent protection as provided in the wording of the claims is not restricted to tomatoes derived from the process as described, but covers all tomatoes with the respective content of flavonol. Thus, the patent can also cover pre-existing plants within the range of flavonol content as claimed.

Further, claims 2-4 are directed to tomatoes with a flavonol content not related to the fruits but to the overall content in the plants, including the leaves. Experts in this field commonly recognise that plant varieties with a high overall content of flavonol were already widely known. (see e.g, Crozier et al., 1997).

There are further complications for the patent holder deriving from the fact that some tomatoes had already been previously created using genetic engineering to achieve a higher content of flavonols in the fruits. Willities et al (2005) attempted to introduce some criteria to make the quality of their tomatoes distinct from those derived from genetic engineering. As a quote already mentioned in another context states:

> "To date, transgenic high flavonoid tomato lines have been created by overexpressing a heterologous CHI gene (Muir et al., 2001) or the maize transcription factors LC and C1 (van Noortlaan et al., 1999; Bovy et al., 2002): In the first strategy, high flavonoid lines were

produced, but accumulation was limited to the peel. In the second strategy, flavonoids were produced throughout the fruit, but the induction of tomato genes by the maize transcription factor was apparently not uniform and led to altered patterns of flavonoid accumulation. The breeding approach outlined in this report resulted in more uniform expression of flavonoid pathway genes and high level accumulation of quercetin in both peel and flesh."

However, no such criteria were introduced into the claims of the patent. Consequently, contrary to the claims in the opposed patent, the tomatoes are not new.

This fact is further substantiated in findings showing that claim 1 of the opposed patent falls within the scope of other patents such as those filed, for example, by Unilever:

In WO 99/37794, claim 17 reads (2008 granted as EP 1049791 with claim 17 being narrowed):

> A tomato plant having enhanced flavonol levels in the flesh of the fruit.

In EP 1254960, claim 1 reads:

> A process for increasing the flavonoid content of a plant wherein said process comprises increasing the activity of chalcone synthase and flavonol synthase therein.

Further, in EP 1254960, claim 5 reads:

> A process of any one of the preceding claims wherein the flavonol content of said plant is increased in leaf tissue and/ or fruit tissue.

Further, in EP 1254960, claim 12 reads:

> A process [of any of the preceding claims as mentioned in claim 11] wherein said plant is a tomato plant.

In WO 2000004175, claim 23 reads:

> A tomato plant having enhanced levels of specific flavonoids in the peel of the fruit compared to the level of flavonoids in the peel of the fruit of untransformed plants.

(5) Art 52 - discovery

In essence, the plant characteristics as described in the patent and the respective genetic conditions as identified do not arise from technical processes, but were found in existing natural biodiversity.

Thus, the patent as granted covers non-patentable matter under Article 52.

(6) Art 83 – disclosure

The patent claims all tomatoes that show a content of flavonol higher than 17 mg/mg dwt in their peel and more than 2 mg/mg dwt in the flesh of the fruits. But the patent does not teach how to produce plants with a higher content beyond 17 mg/mg dwt in the peel and more than 2 mg/mg dwt in the flesh.

Further, the patent shows how to use accession LA 1926 for breeding to enhance the content of flavonol in the fruit up to a level of 17 mg/mg dwt in the peel and up to 2 mg/mg dwt in the fruits. However, no such disclosure is made for accessions LA 2884 and LA 1963, which are apparently different in their genetic and phenotypic conditions (see Willitis et al. 2005). Given the details presented by Willitis et al. (2005), it has to be assumed that any attempt to breed tomatoes with higher content of flavonol in the peel and the fruits is likely to be less successful than using accession LA1926.

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