International Journal of Competitive Intelligence, Strategic, Scientific and Technology Watch
SciWatch Journal 1 (2008), Issue 1, 19 - 53

Analysis of scientific and patent production regarding the treatment of resveratrol.

Víctor Cavaller

Estudios de Ciencias de la Información y de la Comunicación
Universitat Oberta de Catalunya
E-mail: vcavaller@uoc.edu

Keywords
Resveratrol, patents, wine sector, R+D, biotechnology, scienceometrics, bibliometrics, wine making

Abstract
We will focus the analysis in this article in a hypothetical study addressed to companies in the wine-making industry. The objective will be the determination of the competitive advantage that can be obtained if the knowledge that comes from R+D in the biotechnology field is applied.
We will proceed to a cienciometric and bibliometric study of patents, in the context of the application of new technologies, more precisely in the application of the ultraviolet light to increase the concentration of the natural antioxidant resveratrol, which can be found in the grape and then passes on to the wine during the wine making process, and in this process, it develops its beneficial potential effects for the health of the grapes and the wine.

---

1. Introduction

The focus of this article is a hypothetical study of a company in the wine-making, food or pharmaceutical sector, and consists of ascertaining the competitive edge that may be secured through the application of knowledge derived from R&D. The analysis will be a scientometric and bibliometric study of patents in the application of new technologies, specifically in the application of ultraviolet light to increase the concentration of natural antioxidant resveratrol, found in grapes and wine. This develops the potential health benefits of grape and wine.

The objective is to present an example of the sequential application of quantitative, qualitative and relational indicators and finally examine one element, a specific patent. This application overall should allow us to assess the degree of significance of the results obtained.

1.1. resveratrol and polyphenols

Resveratrol belongs to the group of polyphenols. It is a component that is mostly found in the skin and seeds of black grapes and passes into the wine during fermentation (Bujanda, 2001).

Polyphenols are a heterogeneous group of molecules that share the characteristic of having several benzene groups within its structure replaced by hydroxyl functions.

Phenolic compounds in wine include:

- Phenolic acids (coumarin, Cinnamic, caffeic, gentisic, ferulic and Vanillic).
- And flavonoids (catechins galocatechins, Anthocianins, resveratrol and quercitin), which are synthesized by a common metabolic pathway from phenylalanine. Flavonoids can be classified into several families, according to changes in its basic structure: flavones, flavonols, favanoles, antocianidinas and others. These compounds have hydroxyl groups (-OH) attached to its ring structure with high ability to neutralize free radicals harmful to our health.

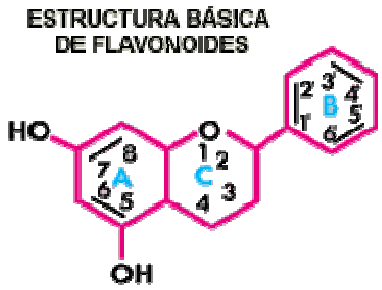


Figure 1: Basic structure of flavonoids
Source: the wine dictionary (2002)

These compounds come, as we have said, from the black grapes and their derivatives (must, wine and champagne), particularly their skin and are produced as a form of protection against the high temperatures to which they are exposed. Small amounts are also found in peanuts and derivatives. They are important to the plants physiology, contributing to the resistance of microorganisms and insects and help preserve its integrity for their continued exposure to environmental stressors, including ultraviolet radiation and high temperatures.

In humans, part of the biological activity of polyphenols is due to its ability to form part of the cellular antioxidant system. The high activity displayed at physiological level, resveratrol, has been linked to the preventive effect on cardiovascular disease and cancer (Romero and Lamuela, 2001).Several epidemiological studies have shown this effect with moderate consumption of wine (Renaud and De Lorgeril, 1992; Renaud and others, 1998; Grønbæk and others, 2000).

1.2. The investigation of applications of resveratrol

With regards to the investigation of the physiological properties of resveratrol we have noted those that have treated it as a cardiovascular protector, which inhibits platelet aggregation and oxidation of LDL (low density lipoprotein) and encourages the protection of vase-dilator substances (Pace-Asia and other, 1995; Frankel and others, 1993; Hsieh and others, 1999). It has also been investigated and was shown to be a potent anti-cancer, inhibiting each stage of tumour formation (Jang et al, 1997). Its performance has been recognized as an antioxidant (Jang et al, 1999) and anti-inflammatory (Jang et al, 1997) and as a phytoestrogen due to its structural similarity to the synthetic estrogens diethylstilbestrol (Gehm et al, 1997) "(Romero and Lamuel , 2001).
Recent studies (Estruch and Urbano, 2005) confirm that resveratrol along with the group of flavonoides is responsible for the relationship between moderate consumption of wine and less heart attacks. The reason lies in the properties of these polyphenols and other components that reducing cholesterol and triglycerides in the blood and make it more fluid, thus preventing the appearance of thrombi. Polyphenols can reduce atherosclerosis by up to 30% and prevent the appearance of low-density cholesterol by 96%. Based on these studies, the properties of resveratrol, and this group of components that are found in grapes and red wine are also antioxidants and anticancerous.
The trans-resveratrol[1] was also known for its contribution to the prevention of cardiovascular diseases and cancer.

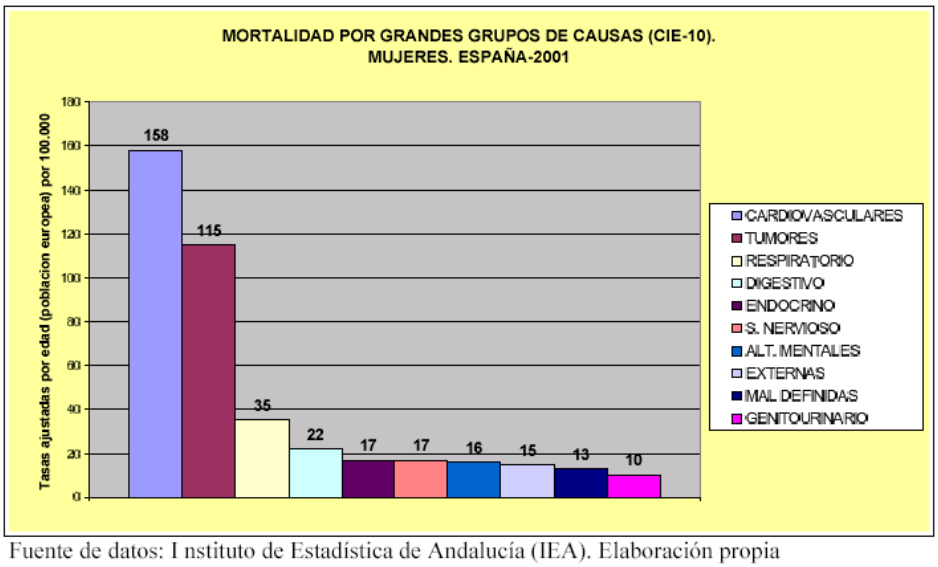
Trans-resveratrol es el nombre comúnmente usado para el *trans*-3,4',5-trihidroxiestilbeno que tiene CAS RN 501-36-0 y fórmula (1). El *trans*-resveratrol es un antioxidante natural que se encuentra en las plantas, muchas de las cuáles son componentes de la dieta humana, como las uvas, los cacahuetes y las moras. Es conocido que el *trans*-resveratrol contribuye a la prevención de las enfermedades cardiovasculares y el cáncer (M. Jang *et al.*, "Cancer chemopreventive activity of resveratrol, a natural product derived from grapes", *Science* 1997, vol. 275, pp. 218-220). Esta protección puede ser atribuible a sus propiedades como antioxidante, antiinflamatorio e inhibidor de la agregación plaquetaria junto con su actividad mixta agonista/antagonista para los receptores de estrógenos (K.P.L. Bhat *et al.*, "Biological effects of resveratrol" *Antioxid. Redox Signal.* 2001, vol. 3, pp. 1041-64; K.P.L Bhat *et al.*, "Estrogenic and antiestrogenic properties of resveratrol in mammary tumor models", *Cancer Research* 2001, vol. 61, pp. 7456-7463). De todos modos, en el estado de la técnica no se menciona o sugiere nada relacionado con el uso del *trans*-resveratrol para el tratamiento de la infertilidad masculina.

Figure 2: Excerpt from the description of properties of trans-resveratrol which reports on the state of the art in the patent application (Nº 200401599)

Source: EPO (2006)

[1] "The resveratrol is a phenolic compound with structural formula has two isomeric forms, cis and trans. Trans-resveratrol was found in the wine for the first time in 1992 by Siemman and Creasy, and in 1993 the presence of the cis isomer was found (Jeandet et al., 1993, Gonzalo et al., 1995). More recently has been the identification of the two isomers glucoside and piceid in wine (Lamuel-Raventós et al., 1995) and cava (Lacueva Andres et al., 2001) "(Romero and Lamuel, 2001). The bibliographic references are from the referred article.

These investigations have added strategic value to the cultivation and processing of wine for commerce and also applications so that has nothing to do with peoples dietary requirements. Commercial expectations on these open lines of research are enormous.
Social studies show health and mortality rates suggest that cardiovascular diseases (ischemic heart disease and coronary disease) as the leading cause of death among the population of developed countries (Heinemann and Heuchert, 2005) therefore remains a priority in the preventive health system to lengthen the life expectancy of its population. This trend is more pronounced in females than in males (Cruz, 2005).



Fuente de datos: I nstituto de Estadística de Andalucía (IEA). Elaboración propia

Figure 3: Mortality in large groups showing causes corresponding to women in 2001. Cardiovascular disease is highlighted as the top cause.
Source: Cruz (2005)


(19) OFICINA ESPAÑOLA DE PATENTES Y MARCAS
ESPAÑA

(11) Número de publicación: **2 245 609**
(21) Número de solicitud: 200401599
(51) Int. Cl.: **A61K 31/05**
A61P 15/08

(12) SOLICITUD DE PATENTE A1

(22) Fecha de presentación: **18.06.2004**
(43) Fecha de publicación de la solicitud: **01.01.2006**
(43) Fecha de publicación del folleto de la solicitud: **01.01.2006**

(71) Solicitante/s: **Universidad de Barcelona**
Centro de Patentes de la UB.
Baldiri Reixac, 4
08028 Barcelona, ES
(72) Inventor/es: **Planas Rosselló, Juana M.;**
Juan Olivé, M. Emilia;
Munuera Garcia, Thais;
González Pons, Eulalia y
Rodríguez Gil, Juan Enrique
(74) Agente: **Segura Cámara, Pascual**

(54) Título: **Nuevo agente terapéutico para el tratamiento de la infertilidad y/o subfertilidad masculina en mamíferos.**

(57) Resumen:
Nuevo agente terapéutico para el tratamiento de la infertilidad y/o subfertilidad masculina en mamíferos.
El *trans*-resveratrol induce un aumento de la concentración de espermatozoides debido a un incremento en su conjunto del tejido espermatogénico. También induce un incremento de la concentración sérica de la hormona estimulante del folículo (FSH), de la hormona luteinizante (LH) y de la testosterona lo que implica una estimulación hipotalámico-hipofisario-testicular. A diferencia de otros medicamentos propuestos para el tratamiento de la infertilidad masculina, el *trans*-resveratrol es útil para el tratamiento de la infertilidad masculina y/o subfertilidad producida por diferentes causas como la infertilidad idiopática, niveles elevados de especies reactivas del oxígeno o alteraciones inflamatorias. Es ventajoso que el *trans*-resveratrol tenga varios mecanismos de acción, ya que la infertilidad masculina y/o subfertilidad generalmente tiene múltiples causas convergentes.

Recently, there have been new uses for trans-resveratrol, as a new therapeutic agent for the treatment of male infertility and / or sub-fertility in male mammals.

Figure 4: Patent application (No. 200401599) from the UB on a second medical indication of the use of trans-resveratrol
Source: EPO (2006)

1.3. Expectations and considerations about the applications of resveratrol

The expectations for the future in relation to the practical applications of resveratrol are very large. And the interest in the subject raises many research activities. For example a recent investigation [2] by a research team from the University of Barcelona published in the Analytical Chemistry Journal (May 2005) was the first to describe the union from polyphenols to LDLs (low Lipoproteins density) in living humans. Still to be investigated in detail are issues on the pharmacokinetic (absorption, concentrations, half-life disposal), biphasic behaviour (positive / negative effect of low / high levels of concentration) level of extrapolation from animal experiments to humans, applications in the field of oncology, hepatology, neurology and others.

Moreover, in viticulture in the field of oenology, there is great interest from producers, appellations of origin, wineries, to determine the concentration of resveratrol in wine, despite the known difficulties to dominate all factors involved (Bujanda, 2001)[3]. Certainly, in this sense, it is important to highlight the role which the different stages of winemaking have on the levels of resveratrol in wine and pieced. Maceration cascarillas levels increase considerably (as resveratrol is found in the husk of grapes), while the use of certain filters can drastically reduce the clarifier (Darias-Martin et al, 2000; soleás et al, 1995; Tobella and Waterhouse, 1996). Moreover, the origin of the grape is crucial in the levels of resveratrol and pieced in wine and cava, so that resveratrol could be considered a chemo taxonomic marker enabling a variety of differences in products (Romero-Perez and others, 1996; Lacueva Andres et al, 2001) "(Romero and Laumela, 2001).

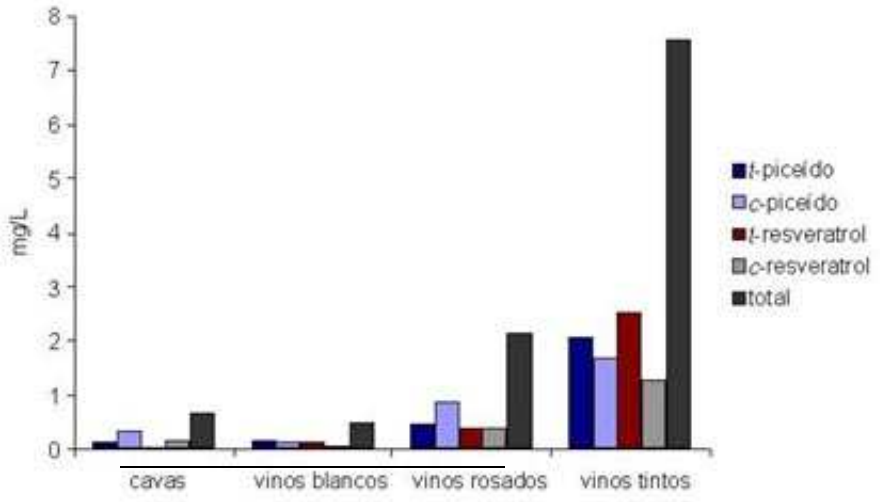


Figure 5: Averages of the isomers of resveratol and pieced in Cavas, white, red and rose wine.

Source: Romero y Laumela (2001)

[2] We refer to: "Uptake of diet resveratrol into the human low-density lipoprotein. Identification and quantification of resveratrol metabolites by liquid chromatography coupled with tandem mass spectrometry". Mireia Urpí-Sardà, Olga Jáuregui, Rosa Maria Lamuela-Raventós, Walter Jaeger, Michaela Miksits, María-Isabel Covas, and Cristina Andres-Lacueva. *Analytical Chemistry*. Vol. 77, No. 10: May 15, 2005. The authors Cristina Andres Lacueva, Mireia Urpí Sardà-and Rosa M. Lamuel-Raventós are part of the Natural Antioxidants and Polyphenols Research Group, Department of Nutrition and Food Science at the Pharmacy Faculty of the University of Barcelona, Olga Jáuregui Cientificotécnicos Services of the UB, and the collaboration of other experts of the Municipal Institute Medical Research-IMIM Barcelona and the University of Vienna (Austria). The research is part of the doctoral thesis of Mireia Urpí-Sardà.

[3] "The measurement of resveratrol in wine is not standardized, so depending on the method or technique used may yield different results. Having used at least four different techniques of HPLC. Of these the most is the standard proposed by Goldberg and Lamuel Raventós-based measurement with diode. " (Bujanda, 2001)

The dose of resveratrol in wine varies highly and depends on many factors such as climate, the level of infection of the grape, how much time must has contact with the skin of grapes, exposure to ultraviolet light, etc. In general, higher humidity, higher degree of infection or attack, the more must contact with the grape juice, increased exposure to ultraviolet radiation and less aging, results in increased amounts of resveratrol. (...) With regards to the development process, "wine made with carbonic maceration has a superior concentration of resveratrol than those made with traditional fermentation". (...).As far as the origin, "wine made from grapes coming from Rioja are superior to Penedès, Navarre or Shore of Duero." As the aging process, when it is aged in oak barrels, the concentration of resveratrol reduces, "between 58% and 68%" (Bujanda, 2001).

At present lines of investigation are being opened in epidemiological studies on the effects of wine consumption in the population, the analysis of the side effects of resveratrol on other levels, and on the methodologies to identify the presence of resveratrol in wine.

1.4. Research projects on the phytochemical substances

Of research projects on the phytochemical substances and their mechanisms of activity so far developed around the world we can mention (Santos-Buelga and Tomas-Barberan, 2004):

- NEODIET (Nutritional Enhancement of Plant Derived Foods in Europe), that has dealt with the constituents of vegetables on health and the possibilities of improving their content in different foods, through treatment or genetic improvement.
- EUROFEDA (European Research on Functional Effects of Dietary Antioxidants), which aims to establish the mechanisms of action of natural antioxidants.
- COST916, on biologically active constituents of the cell wall of plants and their role in nutrition and health.
- POLYBIND, studying the health implications of antioxidant nutrients from the diet in relation to bio availability and colon cancer.

Projects related to the healthy foods in the U.S. are developed in the framework of research centres [4] and laboratories: Antioxidants Research Laboratory, Carotenoids and Health Laboratory, Bone Metabolism Laboratory, Vitamin K Laboratory, Energy Metabolism Laboratory, Obesity and Metabolism Laboratory, Lipid Metabolism Laboratory, Cardiovascular Nutrition Laboratory, Mineral Bioavailability Laboratory, Neuroscience Laboratory, Nutrition and Neurocognition Laboratory, etc.

In Europe, the Institute of Food Research in Norwich (England)[5] should be acknowledged for the development of the following projects: Gastrointestinal Biology and Health, Commensals and Micro flora, Phytochemicals and Health, Micronutrients, Personalised Nutrition, Structuring Foods for Health, Pathogens: Molecular Microbiology, Pathogens: Physiology and Predictive Ecology.[6]

In the field of biotechnology and new technologies for conservation and food processing are developing lines of research on:

- The preservation of foods (biological, physical and chemical processes). For example: procedures to improve the organoleptic characteristics of wine being treated with magnetic fields.
- The acquisition of other food additives. For example: the production of natural antioxidant hidroxitrosol.

[4] Source of information: http://www.hnrc.tufts.edu.
[5] Source of information: http://www.ifrn.bbsrc.ac.uk.
[6] http://www.ifis.org/index.html and http://www.nutrition.org, provide information on research articles on these topics.

- Phytosanitary treatment is therapeutic uses of fruits and vegetables. For example: the application of ultraviolet light to increase the concentration of natural antioxidant resveratrol, found in grapes and wine develops their potential health benefits.

For our case study, we focus on this last line, research projects in the Spanish state, within the National Program of Food Technology, managed by CICYT (Interministerial Commission for Science and Technology). For example:

- The AGL2000-2014 project: "The enhancement of functional juices by enzymatic or physical treatments and the addition of ingredients rich in antioxidants and polyphenols.
- The ALI98-0843 project: "The effect of technological treatments on antioxidants in fruits and vegetables post-harvest, being carried out in the CEBAS (CSIC).

2. Methodological specifications

2.1. Indicators and structure analysis

We are considering in this case the technology and foresight of action for a company whose scope of activity relates to organizational research and development of new products. The deployment method tries to detect the potential of research opportunities.

The aim of this paper is to present both an example of the sequential implementation of quantitative, qualitative, relational and finally to evaluate the case of a specific patent. This case is an example of an elemental indicator.

If we take Callon, Courtial and Penan (1995) as a reference the equivalence between categories of indicators is shown:

According Callon, Courtialyi Penan (1995)		*According to the Author*
Scientometrics		**Informetrics**
Class indicators	Subtypes of indicators	Types of Indicators
Activity indicators	Computation of publications	Quantative
	Computation of citations	Qualitative
Relational indicators of the 1st generation	Key terms and common joint signature articles Citation networks Joint appointments and co-citation	
Relations between Science an Technology	Exerts from articles on patents	Relations
Relational indicators 2nd generation	Concurrent terms of content and analysis of relationships	
Relational indicators 3rd generation	Elemental analysis of detailed content	Rationales

Table 1: ***Equivalence of categories and metric indicators according to the classification of Callon, Courtial y Penan (1995) and the author***

The analysis is focused on the hypothetical study conducted by a company in viticulture, which determines the competitive advantage one might get in the application of knowledge from developed R & D in biotechnology.

A scientometric and patentometric study will be produced on the application of new technologies in the procedures and applications of resveratrol, and of the application of ultraviolet light to increase the concentration of natural antioxidant resveratrol. Research on resveratrol applications (as we have seen, is found in the grape and passed into the wine,

developing the potential health benefits of wine) has resulted in inventions leading to technological empowerment, that has been transferred to companies for marketing.

Analysis of the scientific production and the production of patents of *resveratrol* 1990-2006			
Types of indicators	**Definition of the indicators**	**Purpose of determination**	**Section**
Quantitative Indicators	Calculation of scientific publications and patents and associated uses	Life cycle of research	15.3
Qualitative Indicators	Calculation of scientific publications and patents related to specific uses (grouping common keywords)	Lines of investigation	15.4
Relational indicators	Relational analysis of scientific publications and patents associated with excerpts from articles on patents and patent relating science technology.	Relationship between component, food process, indeed, functional use, and end product associated	15.5
Elemental Indicators	Detailed analysis of content, network events, research, and technology transferred from the Spanish Patent 'No. P.2177465 "Treatment of post-harvest fruit and vegetables by ultraviolet radiation pulses"	List of scientific production and patents associated with research projects and the transfer of technology	15.6

Table 2: ***Phases of analysis, metric indicators used, goals and sections***

3. Analysis of scientific production and patents based on quantitative indicators

3.1. Patents and scientific output in the years 1990-2006 on resveratrol

Calculation of publications is the simplest indicator of activity. The strategy of search and analysis that follow in this section shall be:

a) Annual distribution of scientific output and patents
b) Distribution by types of the scientific output and patents
c) Annual distribution of detailed production[7] of scientific output and patents

a) The parameters of the search procedure to determine the annual distribution of scientific output and patents are:

Keyword: resveratrol
marking dates: 1990-2006
Total records: 2789

[7] The documents as scientific patents in general. In this group the document type Sci-Finder appears as: Journal, General review, Article, Journal_Article, Conference, Meeting abstract, Review, Dissertation, Letter, Announcement News, Online Computer File, Commentary, Computer Optical Disk, Clinical Trial, Evaluation Studies, etc.

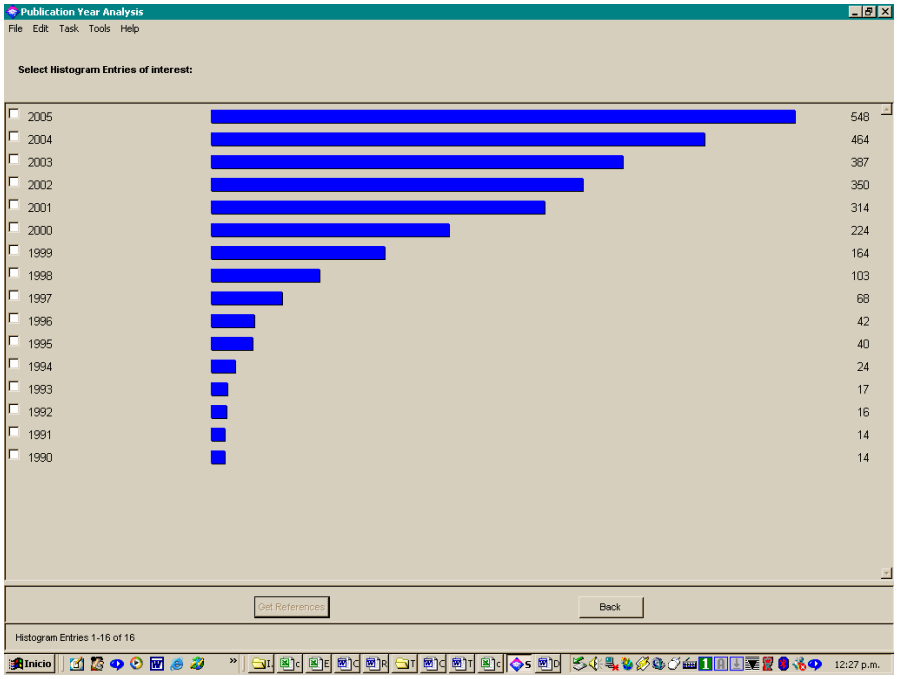


Figure 6: Annual distribution of scientific output and patents on resveratrol between 1990-2005

Source data and graphics: Sci-Finder Scholar (2006)

b) The parameters of the search procedure to determine the distribution by type of document of the scientific output and patents are:

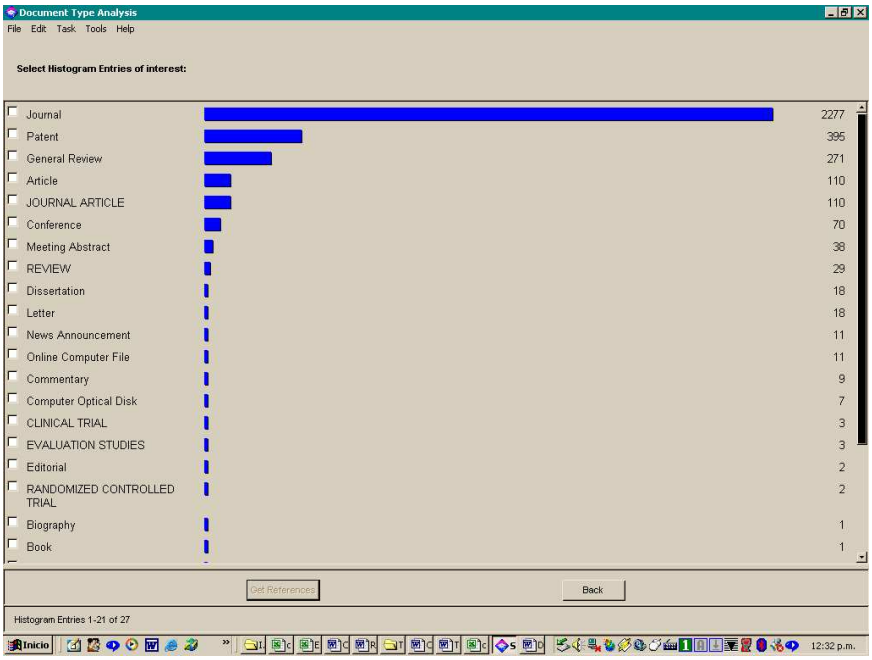


Figure 7: Types of distribution of scientific output and patents on resveratrol between 1990-2005

Source data and graphics: Sci-Finder Scholar (2006)

c) The parameters of the search procedure to determine the annual distribution of scientific output and patents:

	Resveratrol	TOTAL	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	%	
	registres base	**2789**																		
associats a usos	*depurats*	**1238**	0	0	1	3	2	2	7	12	34	77	96	140	184	186	226	268		1238
sobre el total	*publicacions*	**935**	0	0	1	3	2	2	7	9	31	63	73	94	145	140	160	205	76.49	935
	patents	**303**	0	0	0	0	0	0	0	3	3	14	23	46	39	46	66	63	30.73	303

Table 3: Annual distribution of the detailed scientific output and patents of resveratrol between 1990-2005

Source data: Sci-Finder Scholar (2006))

3.2. Patents and scientific output between 1990-2006 in terms of use associated with resveratrol

We can introduce an element added in the publication calculation to determine which investigation activity will be used. The search strategy and analysis that follow in this section shows annual distribution of the detailed scientific output and patents associated with its uses and evolution. The search procedures are defined by the following search parameters:

Locate by substance identifier: resveratrol
Name_CAS: 501-36-00
References associated with use
dates: 1990-2005 Total registers: 1238

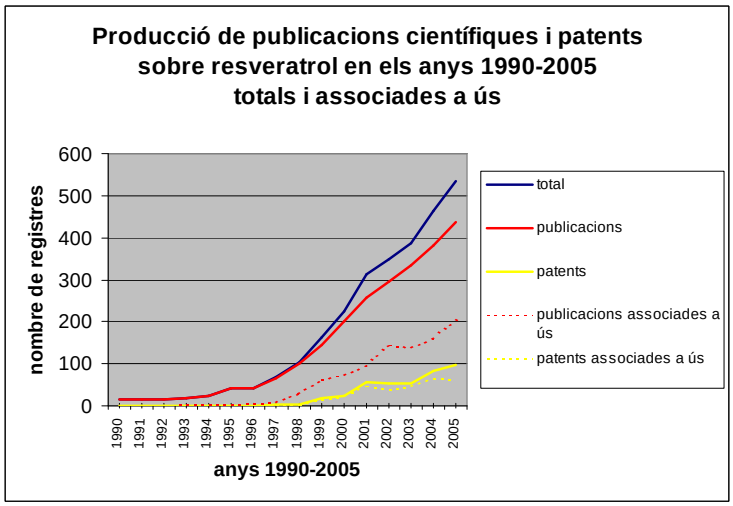
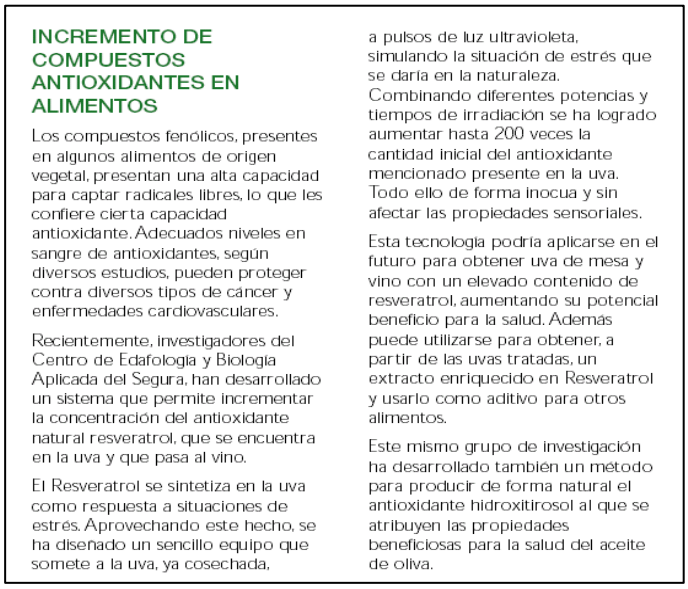


Figure 8: Evolution of the scientific output and patents on resveratrol application between 1990-2005
Source data: Sci-Finder Scholar (2006)

4. Analysis of the scientific output and patents based on qualitative indicators

4.1. Research on the different uses of resveratrol

As shown in the introduction, the research on resveratrol has made known various uses, but has concentrated in certain applications relating to their properties antioxidativas, antitumor, etc.



INCREMENTO DE COMPUESTOS ANTIOXIDANTES EN ALIMENTOS

Los compuestos fenólicos, presentes en algunos alimentos de origen vegetal, presentan una alta capacidad para captar radicales libres, lo que les confiere cierta capacidad antioxidante. Adecuados niveles en sangre de antioxidantes, según diversos estudios, pueden proteger contra diversos tipos de cáncer y enfermedades cardiovasculares.

Recientemente, investigadores del Centro de Edafología y Biología Aplicada del Segura, han desarrollado un sistema que permite incrementar la concentración del antioxidante natural resveratrol, que se encuentra en la uva y que pasa al vino.

El Resveratrol se sintetiza en la uva como respuesta a situaciones de estrés. Aprovechando este hecho, se ha diseñado un sencillo equipo que somete a la uva, ya cosechada, a pulsos de luz ultravioleta, simulando la situación de estrés que se daría en la naturaleza. Combinando diferentes potencias y tiempos de irradiación se ha logrado aumentar hasta 200 veces la cantidad inicial del antioxidante mencionado presente en la uva. Todo ello de forma inocua y sin afectar las propiedades sensoriales.

Esta tecnología podría aplicarse en el futuro para obtener uva de mesa y vino con un elevado contenido de resveratrol, aumentando su potencial beneficio para la salud. Además puede utilizarse para obtener, a partir de las uvas tratadas, un extracto enriquecido en Resveratrol y usarlo como aditivo para otros alimentos.

Este mismo grupo de investigación ha desarrollado también un método para producir de forma natural el antioxidante hidroxitirosol al que se atribuyen las propiedades beneficiosas para la salud del aceite de oliva.

Figure 9: Article on the results of research on the technology involved in the synthesis of resveratrol

Source: OPTI-VT (2002)

In this section qualitative indicators calculate the result of scientific publications and patents related to specific uses. Unlike the previous section where the calculation of those documents to be indexed referencing its specific use (eliminating documents that question or claim, for example an exclusive chemical synthesis procedure). This section, determines the main uses and the corresponding production of those uses. The identification of the specific uses were obtained by gathering and marking and key terms of the analysed records.

Studies of procedures, effects, functional uses y products of resveratol, shows the eagerness of the researchers to achieve greater concentrations of the substance in order to develop functions for foods or nutraceuticals or synthesizer for the provision of drugs or food additives

The strategy of the analysis is carried out in the following phases:

- Classify the scientific publications and patents on resveratrol between 1990-2005 according to keywords
- Select and arrange into 3groups: (1) records associated with the wine or grape (the cultivation, treatments, etc.), (2) records associated with antioxidant properties (3) records associated with antitumor and anti-carcinogenic properties
- Put a limit on records, specifically those associated with use
- Report on the annual distribution from 1990 to 2005, comparing the different groups

4.2. Patents and scientific output in the years 1990-2006 on key terms associated with resveratrol and uses.

- The first phase, Classifying the scientific publications and patents on resveratrol between 1990-2005 according to keywords.

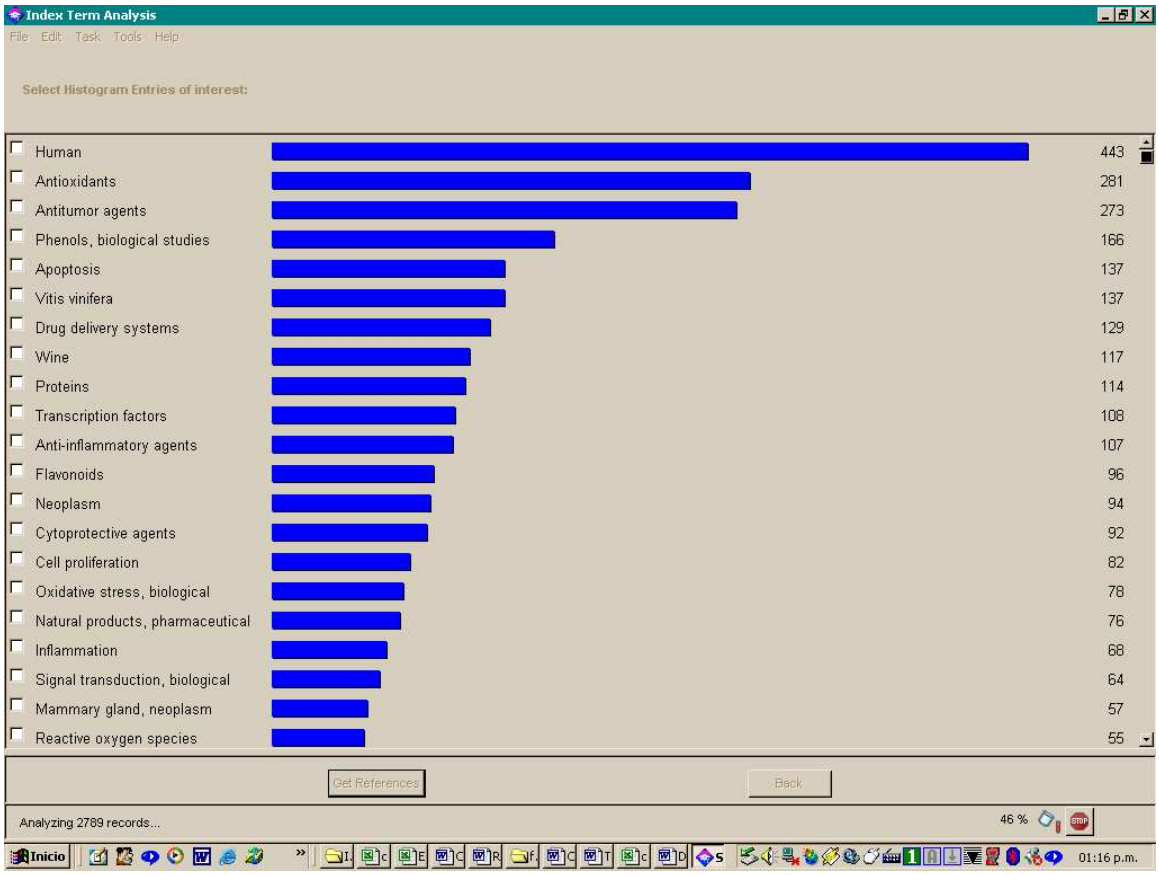


Figure 10: Distribution of key terms of the scientific literature and patents on resveratrol in the years 1990-2005

Source data and graphics: Sci-Finder Scholar (2006)

The results allow us to detect the fringes of the reference to human applications (ranked first), the following specific areas of interest on which research on resveratrol is applied in key terms:

- Documents on the antioxidant properties
- Documents on the antitumor agents, neoplasm, mammary gland, cell profileration, etc.
- Documents on anti-inflammatory agents.

Where the document is indexed in reference to partnerships with biotechnology derived from the wine, the key words are: vitis vinifera, wine, grape.

Continuing on to the second phase, to select and bring together three groups: (1) records associated with the wine or grape (its cultivation, processing, etc.), (2) records associated with the properties antioxidants and (3) records associated with antitumor and anti-carcinogenic properties:

	Resveratrol	TOTAL	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	%	
associats a viti-vinifera o wine o grape	*registres base*	**2789**																		0
	depurats	**701**	3	5	5	8	13	22	27	42	33	49	71	83	67	89	88	96		701
	publicacions	**631**	3	5	5	7	13	22	27	40	33	47	65	70	61	81	71	81	84.38	631
	patents	**70**	0	0	0	1	0	0	0	2	0	2	6	13	6	8	17	15	18.52	70
associats a antioxidant o estrès oxidatiu sobre el total	*registres base*	**2789**																		0
	depurats	**575**	1	0	0	0	0	5	3	8	13	29	55	57	83	91	99	131		575
	publicacions	**477**	1	0	0	0	0	5	3	7	13	28	50	49	73	78	74	96	73.28	477
	patents	**98**	0	0	0	0	0	0	0	1	0	1	5	8	10	13	25	35	36.46	98
associats a antitumor o neoplasma	*registres base*	**2789**																		0
	depurats	**514**	0	0	0	0	0	0	0	4	19	30	38	54	78	85	101	105		514
	publicacions	**424**	0	0	0	0	0	0	0	4	19	27	33	45	65	68	85	78	74.29	424
	patents	**90**	0	0	0	0	0	0	0	0	0	3	5	9	13	17	16	27	34.62	90

Table 5: Annual distribution of scientific output and patents of resveratrol between 1990-2005 associated with wine and/or the grape, antioxidant properties and antitumor properties.

Source data: Sci-Finder Scholar (2006)

The third phase of limiting records, specifically those associated with use.

	Resveratrol	TOTAL	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	%	
associats a usos sobre el total	*registres base*	**2789**																		
	depurats	**1238**	0	0	1	3	2	2	7	12	34	77	96	140	184	186	226	268		1238
	publicacions	**935**	0	0	1	3	2	2	7	9	31	63	73	94	145	140	160	205	76.49	935
	patents	**303**	0	0	0	0	0	0	0	3	3	14	23	46	39	46	66	63	30.73	303
associats a usos relatius al vi	*registres base*	**1238**																		
	depurats	**196**	0	0	0	2	0	2	3	6	6	14	20	23	27	28	32	33		196
	publicacions	**138**	0	0	0	2	0	2	3	4	6	14	14	14	21	22	15	21	63.64	138
	patents	**58**	0	0	0	0	0	0	0	2	0	0	6	9	6	6	17	12	57.14	58
associats a usos antioxidants	*registres base*	**1238**																		0
	depurats	**304**	0	0	0	0	0	0	0	2	5	14	31	27	52	47	54	72		304
	publicacions	**230**	0	0	0	0	0	0	0	1	5	13	26	22	45	35	32	51	70.83	230
	patents	**74**	0	0	0	0	0	0	0	1	0	1	5	5	7	12	22	21	41.18	74
associats a usos antitumorals	*registres base*	**1238**																		0
	depurats	**415**	0	0	1	1	1	0	1	2	14	24	25	45	69	63	83	86		415
	publicacions	**341**	0	0	1	1	1	0	1	2	14	21	21	37	57	48	70	67	77.91	341
	patents	**74**	0	0	0	0	0	0	0	0	0	3	4	8	12	15	13	19	28.36	74

Table 6: Annual distribution of scientific findings and patents of resveratrol between 1990-2005 associated with wine and/or the grape, antioxidant properties and antitumor properties. Source data: Sci-Finder Scholar (2006)

4.3. Comparison of the scientific literature and patents in the years 1990-2006 on key terms associated with resveratrol and uses.

We come finally in fourth stage, to report the annual distribution from 1990 to 2005 comparing the different groups. Here are the results**:**

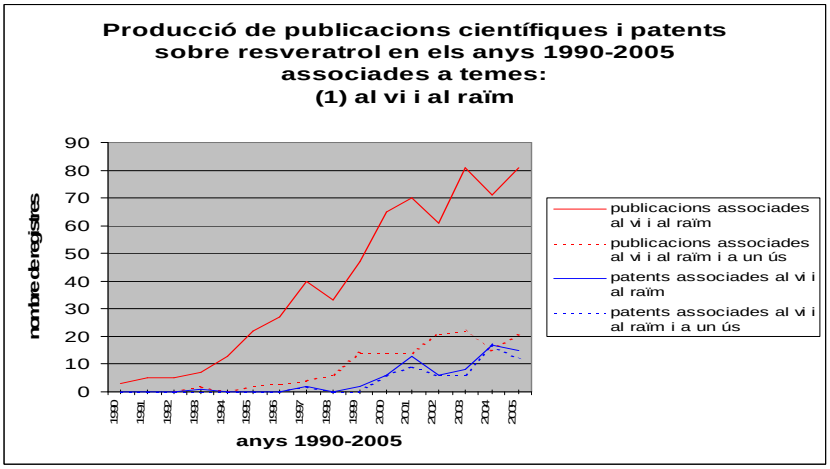


Figure 11: Evolution of scientific output and patents associated with resveratrol and uses to do with wine and / or grapes between 1990-2005

Source data: Sci-FinderScholar (2006)

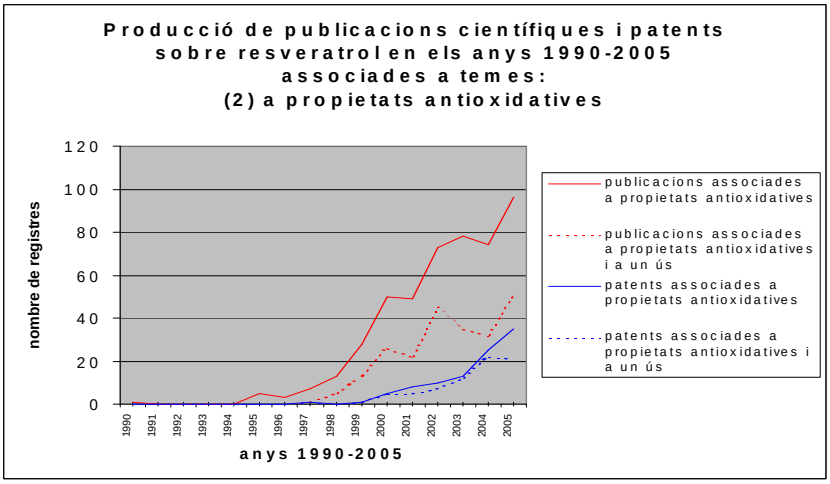


Figure 12: Evolution of scientific output and patents associated with resveratrol and uses to do with antioxidant properties between 1990-2005 Source data: Sci-Finder Scholar (2006)

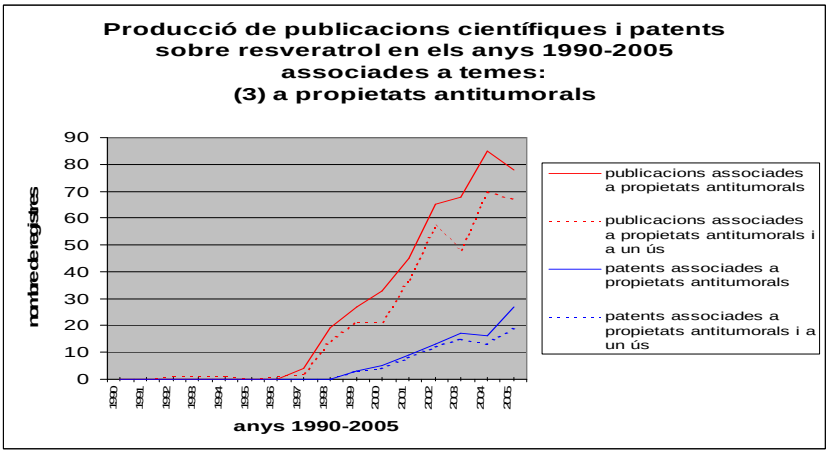


Figure 13: Evolution of scientific output and patents associated with resveratrol and uses to do with anti-tumour properties between 1990-2005 Source data: Sci-Finder Scholar (2006)

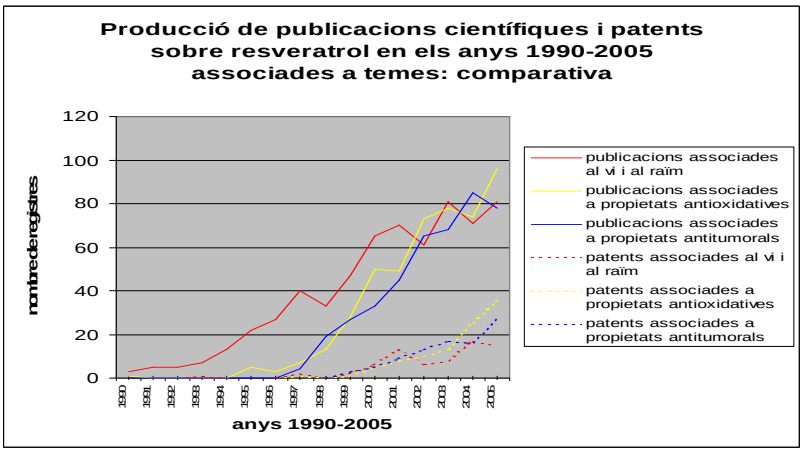


Figure 14: Comparison of the evolution of scientific output and patents associated with resveratrol uses related to wine and / or the grapes, and anti-tumour and antioxidant properties between 1990-2005

Source data: Sci-Finder Scholar (2006)

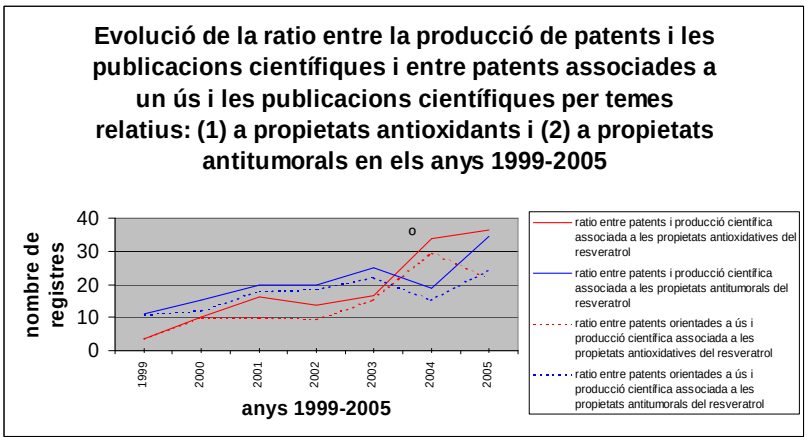


Figure 15: Comparison of the evolution of the ratio between the production of patents and scientific publications about resveratrol and associated with uses

Source data: Sci-Finder Scholar (2006)

4.4. The limitations of qualitative indicators in the analysis of the scientific literature and patents

Using Quantitative indicators, and a simple calculation of publications, the dynamism of a scientific field or the relationship between patents and scientific output in a scientific, technical or related technology to certain key words or uses can be shown. Qualitative indicators are working from information contained in the records of a scientific paper or a patent, or from the relationship between citations in the case of scientific production. Qualitative indicators can't facilitate, for example, classification by source or subject of the scientific literature and patents. Calculations that consider these quality characteristics can only vision general indicators and in some cases are distorted. Particularly, the patent literature is an example of information that is resistant to quantitative analysis, if the aim is to avoid getting into the contents of the documents.

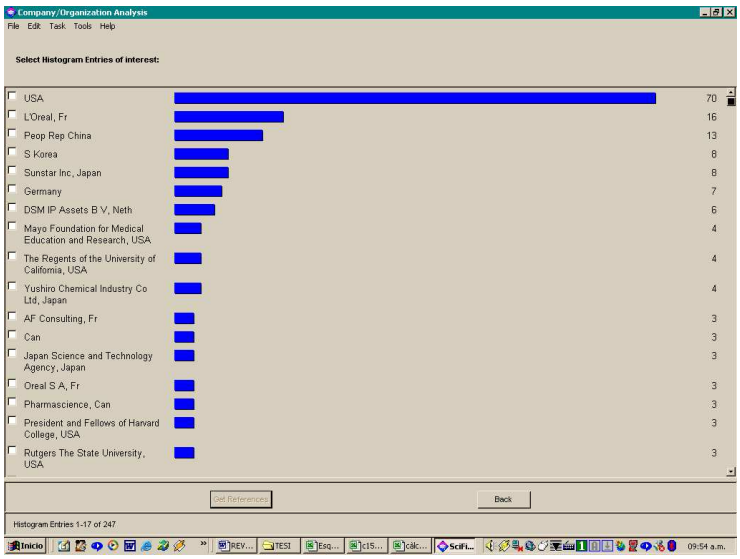


Figure 16: Approach to the distribution of patent applicant on resveratrol resveratrol between 1990-2005

Source data and graphics: Sci-Finder Scholar (2006)

There are differences in the strategies adopted by companies and the laws regarding the registration of patents. There are also different countries in the information systems of patent databases in relation to information and communication. Companies or applicants and inventors have the difficult task of preparing, cleaning and processing of data for analysis

The dataset features from casuistic and heterogeneous particulars. For example, for exact identification of the actors, dates and availability of inventions, one must know what's in the U.S.
It must be patented by the inventor. Patent rights are determined by the date of invention, not the date of the application, which only be issued by the applicant himself.

Qualitative indicators will to classify roughly the thematic lines of inquiry from the subject of documentary records using key terms. However the thematic codes of the CIP (International Patent Classification) that describe the invention in the U.S. also need to be looked at. They are assigned by automated translation of the codes of the classification itself, which is a source of errors.

Qualitative indicators also called relational indicators of the 1st generation (Callon, Courtial and Penan, 1995), for example, the method of joint appointments. These calculations, when we want to extend the patent literature with topic reference or practice, are not a well-established encryption and are an unreliable tool.

Ultimately, the use of these calculations in patent literature for thematic indirect classification, or for the identification and grouping of the actors is an unsound tool and only provides a rough picture.

5. Analysis of scientific patent research based on relational indicators
5.1. Research on the development of the concentrations of resveratrol

Scientific research and technology innovation is in the production of patents. Scientific research in this regard does not focus only on innovative products, but new procedures for obtaining goods or synthesis of new applications or utilities.

In scientometrics, relational indicators (second-generation relational according to Callon, Courtial and Penan) conform to the technical content in dealing with advanced methods such as analysis of associated words (co-word analysis) (Callon, Courtial and Penan, 1995). However, scientific research that supports the patent technically is not just about the component itself, resveratrol, but on the treatment of the product and the natural production that contains the summary procedure, the effect, the functional use and the final product result.

With this higher level and careful analysis of the scientific literature that supports the patent, we are not interested in information that may result from the calculations of the records associated with a use or a specific term. This is not just to consider the relationship between science and technology, based on qualitative indicators that work on scientific publications and citations from patents in order not to identify the interactions between scientific and technical fields, but also to structure content.

In order to draw the structure that describes the content of scientific research, we must realise when we are starting an investigation looking into a substitute for food or natural products that include them, on the procedures or treatments one might apply to obtain a certain effect or another, resulting in a functional use, and on what product is the depositary of the final invention (a drug, an additive, a functional food). The framework of this application remains open. In this sense, the claims in the final edited text of a patent application for reference say: "use resveratrol (isolated from grapes and derivatives) obtained according to previous vindications to enrich foods, to administer as a nutraceutical supplement or for its use in therapeutic formulations" (WO02/085137A1).

We are now interested in the content of scientific research, including scientific publications and patents, using excerpts from articles on patents. In this sense we speak of those who agree the relational indicators relate to the content associated with science and technology.

The references that include reports on the state of the art and the description of the invention in the case of patents are not a result of systematic and quality, they are heterogeneous. History shows that the interests affected by allegations of infringement and other claims.

Therefore, one must read a summary of the documents in order to represent an approximation of the major relational classifications derived. In order to not repeat the content, the following selection of documents that describes much of the research associated with resveratrol under different parameters.

Public No. of the patent	Year application was presented	International classification	Title
ES2207287	1998	A61K31/22, A61K31/205A 61K35/78, A23L1/302, A61P25/00	USE OF CARNITINE AND RESVERATROL TO PRODEUCE A COMPOSITION FOR THE PREVENTION OR THERAPEUTIC TREATMENT OF BRAIN PRODUCED BY AGING AND DRUGS NEUROTOXICITY
ES2167179	1999	A01N31/16	METHOD FOR STRENGTHENING THE GRAPE RIPENING AND ITS INFECTION BY THE IMPLEMENTATION OF EXTERNAL RESVERATROL
ES2170006	2000	C12P7/22, A23L1/30	ENZYMATIC SYNTHESIS OF ANTIOXIDANT HIDROXITIROSOL
ES2169704	2000	A01N31/16	METHOD FOR STRENGTHENING OF TOMATOES, OTHER FRUITS AND VEGETABLES AND ITS INFECTION BY THE IMPLEMENTATION OF EXTERNAL RESVERATROL
ES2177465	2001	A23L1/025, A23L3/28	POSTHARVEST TREATMENT OF FRUITS AND VEGETABLES BY PULSES ULTRAVIOLET RADIATION
ES2190771	2002	C12N5/04, C12N5/14	PROCEDURE FOR THE PRODUCTION OF RESVERATROL, CELL CULTIVATION
WO02083835	2002	C12H 1/16	PROCEDURES TO IMPROVE THE ORGANOLEPTIC CHARACTERSITICS OF THE WINE: TREATMENT WITH MAGNETIC FIELDS
ES2241480	2004	A23L1/025, A23B7/148, A23L3/3418	METHOD FOR INCREASING THE CONTENT OF TRANS-ENDOGENOUS RESVERATROL UVAS BY TREATMENT IN SHORT ANOX
ES2245609	2004	A61K31/05, A61P15/08	NEW THERAPEUTIC AGENTS FOR THE TREATMENT OF INFERTILITY AND/OR SUB-FERTILITY IN MALE MAMMALS

Table 7: ***Collection of patents tested with no indication of publication, classification and title, and chronologically ordered***

Source data: OEPM y WIPO (2006)

Establishing quantitative measures in the relationship of scientific concepts in general and patents in particular from the complex morphology of a research field or a technical field, can be very difficult. The great diversity of topics coupled with other issues the development of strategic diagrams that give us a representation of the structure of the research area. If we look at the description of codes of the international classification of patents[8] we have proof of that.

[8] "International Patent Classification (IPC) is a hierarchical system where the area of technology is divided into a number of sections, classes, subclasses and groups. This system is essential to retrieve patent documents in the search for an invention or determining the state of the art in a specific field of technology. The rating is subject to periodic review to improve the system and take into account the evolution of technology. This edition of the IPC, is the seventh, will be valid until December 31, 2005. The eighth edition of the IPC will enter into force on 1 January 2006" (WIPO, 2006).

A01	AGRICULTURE, FORESTRY, RAISE; HUNTING; CAPTURE; FISHING
A01N	CONSERVATION human or animal body or plant; BIOCIDES, p. ex. BEING DISINFECTANTS, pesticides, herbicides (preparations for medical, dental or toilet, methods and apparatus for disinfection and sterilization in general, or for air deodorization
A23	FOODS OR FOOD PRODUCTS, THIER TREATMENT, NOT COVERED BY OTHER CLASSES
A23L	FOOD, FOOD PRODUCTS OR NON-ALCOHOLIC BEVERAGES NOT COVERED BY SUBCLASSES (...); TREATMENT OR ITS PREPARATION, p. ex. COOKING, MODIFICATION OF NUTRITIONAL QUALITIES, PHYSICAL TREATMENT; FOOD STORE OR FOOD IN GENERAL (preservation of flour or masses bread making)
A23L 1/025	Physical treatment, p. ex. wave energy, irradiation, means electric, magnetic fields (cooking, conservation, etc.)
A 61	Medical and veterinary sciences; HYGIENE
A61K	PREPARATIONS FOR MEDICAL USE, OR FOR DENTAL CLEANING
A61K 31/00	Pharmaceutical Preparations: Characterized by the active substance. Organic substances.
C12	BIOCHEMISTRY; BEER, ALCOHOLIC BEVERAGES, WINE, VINEGAR; MICROBIOLOGIA; Enzymology; TECHNIQUES OF GENETIC CHANGE
C12N	MICROORGANISMS OR ENZYMES
C12N 5/00	MICROORGANISMS; SPORES; cells differentiated VIRUS
C12H	Pasteurization, sterilization, conservation, purification, clarification, AGING OF ALCOHOLIC DRINKS OR REMOVAL OF ALCOHOL
C12P	Fermentation process or processes that ENZYMES USED FOR SYNTHESIS OF A CHEMICAL COMPOUND OR BECAUSE OF COMPOSITION DATA, OR FOR THE SEPARATION OF OPTICAL ISOMERS FROM A racemic mixture

Table 8: *Description of content associated with the codes of the international classification of patents for the collection of selected patents*
Source data: WIPO (2006)

5.2. Relational structure content

In scientometrics, to define the relational structure of content, apart from the above method based on multiple terms, is the method of joint classification. This method is based on classification codes associated with the patent documents that provide a word or words that describe part of the content of the publication.
key concepts identified in terms of classification can provide a concise and simplified morphology of the network and research stakeholders involved in its production.[9]

In this case, we use the classification code and the content analysis of the patents to obtain relational structure adopting the following strategy of analysis divided into three phases:

1. Identification of research stakeholders
2. Identification of the parameters when laying claim to the invention
3. Designing the structure of relational content

[9] In the present case is not practical to analyze massive sets of documents related to completed research on resveratrol, and therefore will not take into account neither the frequency nor intensity of the joint appearance of the descriptors associated with areas of research on inventions, that could represent a strategic map of the research topics. We simply present the relational structure of the parameters that describe the contents involved component, treatment procedures, obtaining or synthesis, effects and uses applied.

1) Identification of the origin of the holder of patents in relation to the scope of the search partner.

Publication No. Of the patent	Applicant for the patent holder	General research field of the invention
ES2207287	Laboratorio Sigma-Tau Healthscience S.p.a. (Italia)	A61,A23: medicine and food
ES2167179	Universidad Complutense de Madrid (España)	A01N: agriculture
ES2170006	Consejo Superior de Investigaciones científicas (España)	C12,A23: biochemical and food
ES2169704	Universidad Complutense de Madrid (España)	A01N: agriculture
ES2177465	Consejo Superior de Investigaciones científicas (España)	A23: food
ES2190771	Universidad de Alicante (España)	C12: biochemical
WO02083835	Lutzker, R.S. (EUA)	C12: biochemical
ES2241480	Universidad Complutense de Madrid (España)	A23: food
ES2245609	Universitat de Barcelona (España)	A61: medicine

Table 9: Indication of the applicant for the patent holder selected

Source data: OEPM y WIPO (2006)

2) By analyzing the content of the patent we can identify the parameter object and content of the patent. The parameters and functional use[10] differentiate the claims towards the patent.

Parameters	Content object	Document	Year
Product	Hidroxitirirosol	Patent_NPP: ES2170006	2000
	Resveratrol	Patent_NPP: ES2177465	2001
Food	Grape/wine		
	Oil	Patent_NPP: ES2170006	2000
Procedure	Ultraviolet raddiation	Patent_NPP: ES2177465	2001
	Cell cultivation	Patent_NPP: ES2190771	2002
	Short anoxic treatments	Patent_NPP: ES2241480	2004
Effect	Increased concentration	Patent_NPP: ES2177465	2001
	Collection summary	Patent_NPP: ES2190771	2002
	Improved organoleptic features	Patent_NPP: WO0208385	2002
Functional use	Antioxidant	Patent_NPP: ES2207287	1998
	Plant resistance (tomato, grape, etc)	Patent_NPP: ES2167179, ES2169704	1999 2000
	Infertitlity treatment	Patent_NPP: ES2245609	2004

Table 10: example of alignment between the content objects with products, food products, processes, effects and functional uses of inventions in patent documents examined

Source data: OEPM y WIPO (2006)

[10] Regarding functional uses and the application of new food preservation technologies, from 2002, The US Department of Agriculture stated that irradiation is approved for imported products. The Animal and Plant Health inspection service of the aforementioned Department, has established regulations that prescribe the use of irradiation as a phytosanitary treatment for fruits and vegetables imported into the U.S. (...) this is a measure of protection from various pests". (OPTI_VT, 2002). We know the patent application WO02098471 of Surebeam Corporation System and method for irradiating food and make them safe for consumption. "

3) Finally, the relational diagram represents the connection between the parameters used when researching resveratrol. Components of a particular food, linked to a procedure or treatment, and a functional use.

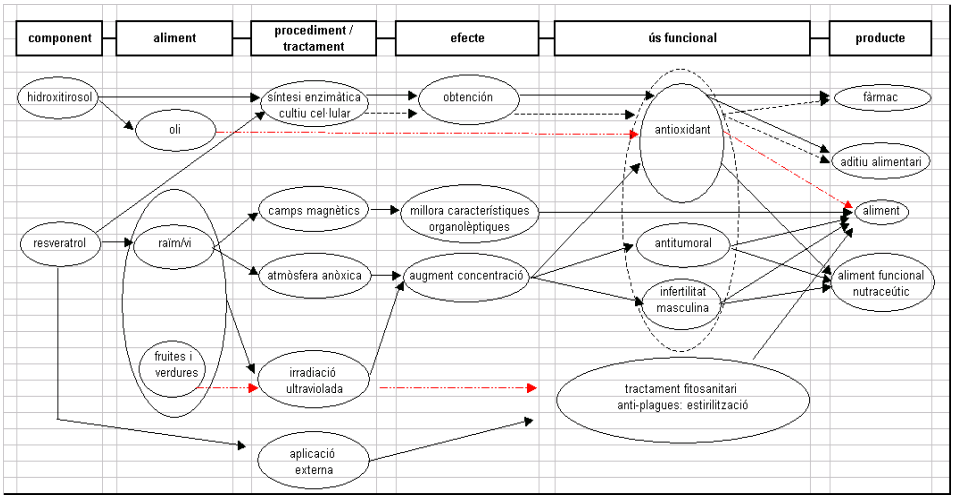


Figure 17: Diagram of relationships between components, foods, procedures and treatments in order to discover the effects, functional uses and products associated with resveratrol research

6. Analysis based on elemental indicators: a case study

Looking at what we have discovered in the past sections (Caballero, 2007ª, 2007 b), relational or elemental indicators (Scientometrics, patentometria and relational also used in 3rd generation) are based on methods that try and quantify the different ways of assessing the reality of a population. They try integrating the unique constituent element of reality as a measurement tool. The indicators draw upon a rational network of agents of the universe. Patentometria are considered third-generation relational indicators. The patent family[11] is an elemental indicator. Appointments are not considered or referred to as the key concepts. They are contained in the reports, but the patent is viewed as occupying a position on a map as a structured network model. The significance of the patent is a summary of information already given.

Elements of this group of indicators can be added in specific cases of patent documents, and the national and international research funding that enabled the progress of a particular line of research should lead to the invention. Other patents that have a technical foundation should also be considered. Finally businesses and products that have developed the technology transferred can be added.

The previous section addressed the analysis of scientific innovation, in a group we referred to as patent relational indicators, responding to the parameters that define a research on a particular component. In this section, an element of the network (a patent) is selected, and then the diagram of elements that explain their constitution is drawn.

We chose the patent recorded in the presentation of OEPM (Oficina española de Patentes y Marcas) on the 19 of April 2001 by the Superior Council of Scientific Research, under "Postharvest treatment of fruit and vegetables using pulses of ultraviolet irradiation". The inventors are Francisco Tomás Barberán, Juan Carlos Espín de Gea and Emma Cantos Villar. Researchers from *Centro de Edafología y Biología Aplicada del Segura* (CEBAS) affiliated with *Consejo Superior de Investigaciones Científicas* (CSIC).

Our strategy of investigation and analysis consist of:

1) Consider the sequence of the records and the elements involved in its formation, in order to analyze their life cycle.

2) Determine the documents fundamental to the scientific research and associated inventions, by examining the documents cited in the report, as significant international research in the document cited in the patent and scientific article that disseminates the contents of the invention.

3) Represent the whole of the relationship of national and international research funding from CEBAS (CSIC), with documents of the scientific production of researchers registered to this centre, and that have made progress in a particular line of research that has led to the invention and technology transfer to companies that exploit the same invention.

[11] "The patent family includes the patents filed in different countries for the same invention. Equivalent patents are those that belong to the same family. Knowledge of the patent family is essential to know in which countries have patent protection "(Zeal, 2006).

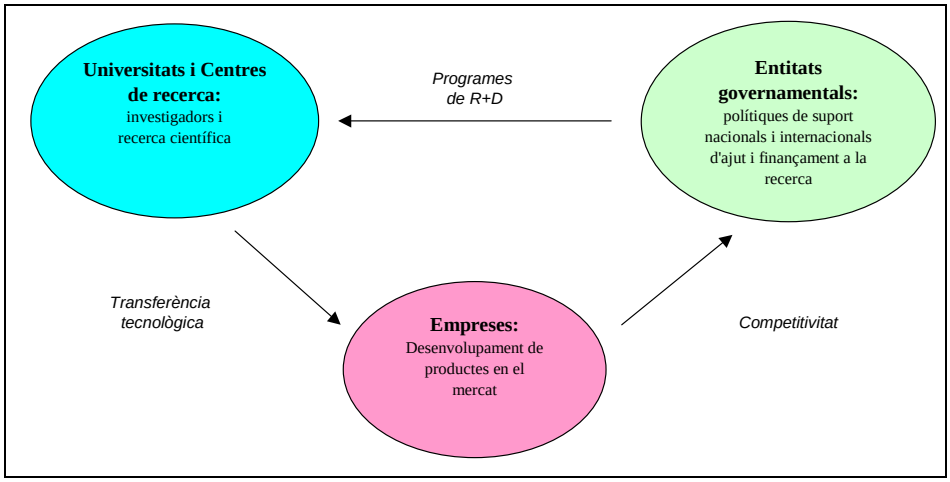
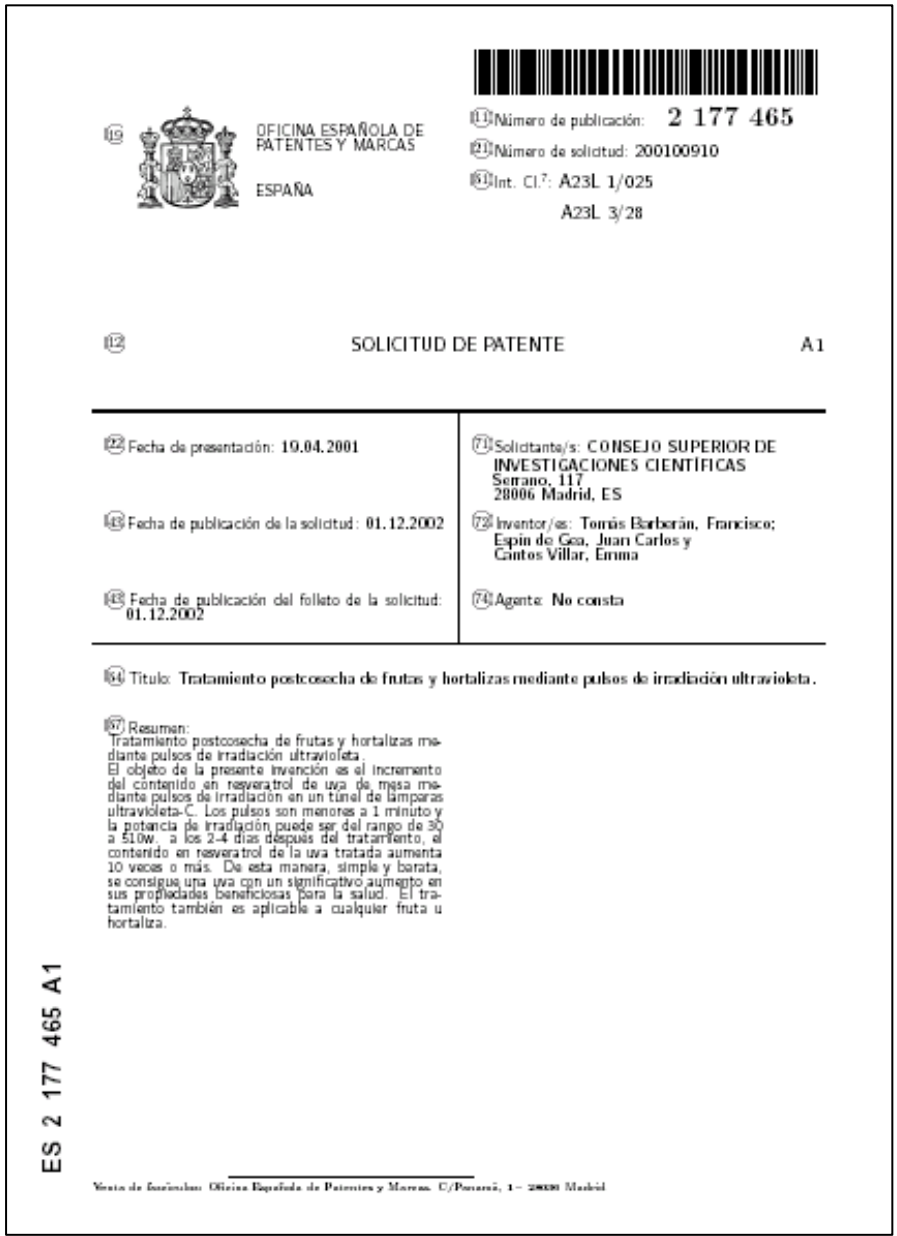


Figure 18: Triple node of R+D: government, university, business



(19) OFICINA ESPAÑOLA DE PATENTES Y MARCAS
ESPAÑA

(11) Número de publicación: **2 177 465**
(21) Número de solicitud: 200100910
(51) Int. Cl.[7]: A23L 1/025
A23L 3/28

(12) SOLICITUD DE PATENTE A1

(22) Fecha de presentación: 19.04.2001
(43) Fecha de publicación de la solicitud: 01.12.2002
(45) Fecha de publicación del folleto de la solicitud: 01.12.2002

(71) Solicitante/s: CONSEJO SUPERIOR DE INVESTIGACIONES CIENTÍFICAS
Serrano, 117
28006 Madrid, ES
(72) Inventor/es: Torrás Barberán, Francisco;
Espín de Gea, Juan Carlos y
Cantos Villar, Emma
(74) Agente: No consta

(54) Título: Tratamiento postcosecha de frutas y hortalizas mediante pulsos de irradiación ultravioleta.

(57) Resumen:
Tratamiento postcosecha de frutas y hortalizas mediante pulsos de irradiación ultravioleta.
El objeto de la presente invención es el incremento del contenido en resveratrol de uva de mesa mediante pulsos de irradiación en un túnel de lámparas ultravioleta-C. Los pulsos son menores a 1 minuto y la potencia de irradiación puede ser del rango de 30 a 510w. a los 2-4 días después del tratamiento, el contenido en resveratrol de la uva tratada aumenta 10 veces o más. De esta manera, simple y barata, se consigue una uva con un significativo aumento en sus propiedades beneficiosas para la salud. El tratamiento también es aplicable a cualquier fruta u hortaliza.

ES 2 177 465 A1

Venta de fascículos: Oficina Española de Patentes y Marcas. C/Panamá, 1 – 28071 Madrid

6.1. The research for technology transfer and patent ES-2177465

The patent is dated April 19, 2001 while the OEPM publication date December 1, 2002. The scientific paper cited in the patent application of the members of the same research group considered significant date of October 2000 is:

- Cantos, E.; Garcia-Viguera, C.; de

Pascual-Teresa, S.; Tomas-Barberan, F. A (2000) " Effect of postharvest ultraviolet irradiation of Resveratrol and other phenolics of Cv.Napoleon table grapes". Journal of Agricultural and Food Chemistry, October, Volume. 48, nº 10, pages 4606-4612.

Figure 19: Publication of the patent application ES-2177465
Source: OEPM (2002)

Throughout 2002 the group members promoted their invention:

R+D CSIC

Alimentos enriquecidos en compuestos antioxidantes

23 de octubre de 2002

Investigadores del Centro de Edafología y Biología Aplicada del Segura de Murcia (CEBAS) del CSIC han desarrollado un sistema que permite incrementar la cantidad de un antioxidante natural presente en la uva y que pasa al vino, y otro sistema para producir de forma natural un antioxidante presente en el aceite de oliva.

Los alimentos de origen vegetal contienen una serie de factores no nutricionales que tienen capacidad de protección contra ciertas enfermedades, entre los que se encuentran los compuestos fenólicos caracterizados por su alta capacidad de captar radicales libres (actividad antioxidante). Numerosos estudios han demostrado que unos adecuados niveles en sangre de antioxidantes pueden proteger contra diversos tipos de cáncer y enfermedades cardiovasculares. Se sabe además que alimentos típicos de la dieta mediterránea como el aceite de oliva y el vino tinto contienen en su composición polifenoles antioxidantes.

Investigadores del Centro de Edafología y Biología Aplicada del Segura (CEBAS) han desarrollado un sistema que permite incrementar la concentración de un antioxidante natural presente en la uva y que pasa al vino.

El vino tinto contiene en su composición el antioxidante resveratrol. Esta molécula se ha asociado con las propiedades beneficiosas para la salud que se atribuyen a un consumo moderado de vino tinto. Se sabe que este antioxidante está presente en las uvas. El equipo dirigido por Francisco Tomás-Barberán, responsable del grupo de Calidad, seguridad y bioactividad de alimentos de origen vegetal del CEBAS, ha aprovechado el hecho de que este antioxidante se sintetiza en la uva como respuesta a situaciones de estrés para diseñar un procedimiento capaz de estimular su biosíntesis. Se trata de un equipo muy sencillo que lo que hace es someter a la uva, una vez cosechada, a pulsos de irradiación ultravioleta. «De este modo simulamos una situación de estrés que se da en la naturaleza, con la ventaja de que nosotros podemos controlarlo» explica Juan Carlos Espín, miembro del grupo de investigación. "Combinando diferentes potencias y tiempos de irradiación hemos obtenido resultados muy prometedores, ya que hemos sido capaces de aumentar hasta más de 200 veces la cantidad inicial de este antioxidante en uva de una manera inocua y sin afectar sus propiedades sensoriales de la uva".

El proceso también permite obtener extracto del antioxidante natural resveratrol para utilizarlo como aditivo en otros alimentos

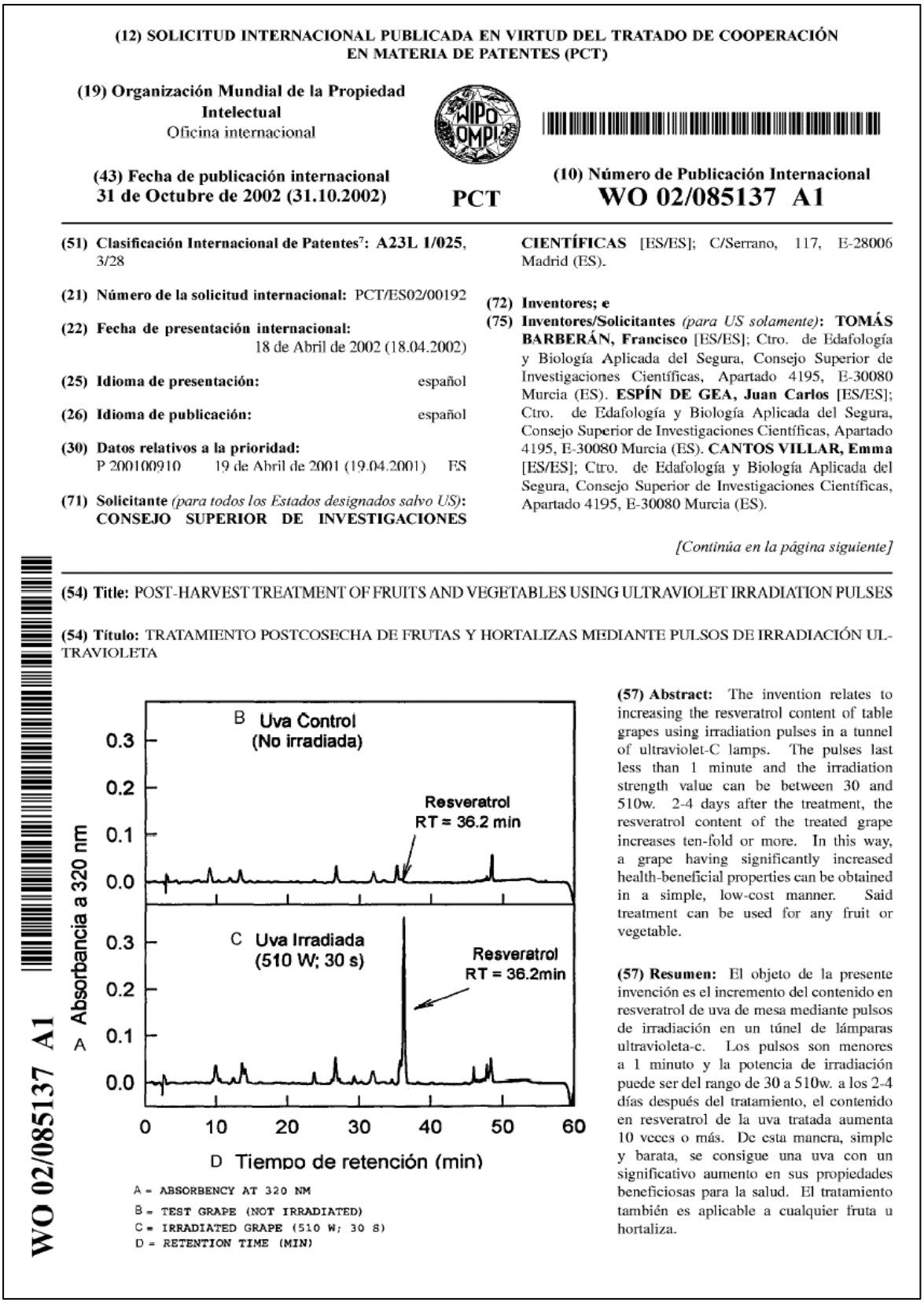
Esta tecnología, que ha sido patentada, permitiría obtener uva de mesa y vinos con un elevado contenido en este antioxidante natural y por lo tanto con sus propiedades beneficiosas para la salud mejoradas. Asimismo, se puede obtener un extracto enriquecido en resveratrol a partir de las uvas tratadas y utilizarlo como aditivo para otros alimentos.

También con el aceite de oliva

Figure 20: Article about the results of the investigation developed for CEBAS (CSIC) about the applied technology of resveratrol

Source: R+D_CSIC (2002)

The international application published under the Cooperation Treaty (PCT) WO 02/085137 for the international extension of the Spanish patent ES-2177465 is April 18, 2002, a day before the deadline to exercise the right of priority, and is published October 31, 2002. On the 11 of October, 2002 an amendment to the claims original document which is annexed to the full publication was presented to the international patent office.



(12) SOLICITUD INTERNACIONAL PUBLICADA EN VIRTUD DEL TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES (PCT)

(19) Organización Mundial de la Propiedad Intelectual
Oficina internacional

(43) Fecha de publicación internacional
31 de Octubre de 2002 (31.10.2002)

PCT

(10) Número de Publicación Internacional
WO 02/085137 A1

(51) Clasificación Internacional de Patentes[7]: A23L 1/025, 3/28

(21) Número de la solicitud internacional: PCT/ES02/00192

(22) Fecha de presentación internacional:
18 de Abril de 2002 (18.04.2002)

(25) Idioma de presentación: español

(26) Idioma de publicación: español

(30) Datos relativos a la prioridad:
P 200100910 19 de Abril de 2001 (19.04.2001) ES

(71) Solicitante *(para todos los Estados designados salvo US)*: CONSEJO SUPERIOR DE INVESTIGACIONES CIENTÍFICAS [ES/ES]; C/Serrano, 117, E-28006 Madrid (ES).

(72) Inventores; e

(75) Inventores/Solicitantes *(para US solamente)*: **TOMÁS BARBERÁN, Francisco** [ES/ES]; Ctro. de Edafología y Biología Aplicada del Segura, Consejo Superior de Investigaciones Científicas, Apartado 4195, E-30080 Murcia (ES). **ESPÍN DE GEA, Juan Carlos** [ES/ES]; Ctro. de Edafología y Biología Aplicada del Segura, Consejo Superior de Investigaciones Científicas, Apartado 4195, E-30080 Murcia (ES). **CANTOS VILLAR, Emma** [ES/ES]; Ctro. de Edafología y Biología Aplicada del Segura, Consejo Superior de Investigaciones Científicas, Apartado 4195, E-30080 Murcia (ES).

[Continúa en la página siguiente]

(54) Title: POST-HARVEST TREATMENT OF FRUITS AND VEGETABLES USING ULTRAVIOLET IRRADIATION PULSES

(54) Título: TRATAMIENTO POSTCOSECHA DE FRUTAS Y HORTALIZAS MEDIANTE PULSOS DE IRRADIACIÓN ULTRAVIOLETA

(57) Abstract: The invention relates to increasing the resveratrol content of table grapes using irradiation pulses in a tunnel of ultraviolet-C lamps. The pulses last less than 1 minute and the irradiation strength value can be between 30 and 510w. 2-4 days after the treatment, the resveratrol content of the treated grape increases ten-fold or more. In this way, a grape having significantly increased health-beneficial properties can be obtained in a simple, low-cost manner. Said treatment can be used for any fruit or vegetable.

(57) Resumen: El objeto de la presente invención es el incremento del contenido en resveratrol de uva de mesa mediante pulsos de irradiación en un túnel de lámparas ultravioleta-c. Los pulsos son menores a 1 minuto y la potencia de irradiación puede ser del rango de 30 a 510w. a los 2-4 días después del tratamiento, el contenido en resveratrol de la uva tratada aumenta 10 veces o más. De esta manera, simple y barata, se consigue una uva con un significativo aumento en sus propiedades beneficiosas para la salud. El tratamiento también es aplicable a cualquier fruta u hortaliza.

WO 02/085137 A1

Figure 21: International publication under the Cooperation Treaty (PCT) WO 02/085137 for the international extension of the Spanish patent ES-2177465
Source: WIPO (2002)

The scientific documents of members of the same group of researchers considered significant in the investigation report of the international patent application WO 02/085137 are the

immediately preceding (aformentioned) and immediately after October 2001 published the results of the invention in the patent application. The references to it are:

Cantos, Emma; Espin, Juan Carlos; Tomas-Barberan, Francisco A. (2001) "Postharvest induction modeling method using UV irradiation pulses for obtaining resveratrol-enriched table grapes: a new 'functional' fruit?". Journal of Agricultural and Food Chemistry, October, Volume 49(10), pages 5052-5058. CODEN: JAFCAU ISSN:0021-8561. CAN 135:343592 AN 2001:636476 CAPLUS
Locating the Sci-Finder of the documents reference promotes the invention:

Bibliographic Information

Postharvest Induction Modeling Method Using UV Irradiation Pulses for Obtaining Resveratrol-Enriched Table Grapes: A New "Functional" Fruit? Cantos, Emma; Espin, Juan Carlos; Tomas-Barberan, Francisco A. Laboratorio de Fitoquimica Departamento Ciencia y Tecnologia de Alimentos, CEBAS-CSIC, Murcia, Spain. Journal of Agricultural and Food Chemistry (2001), 49(10), 5052-5058. Publisher: American Chemical Society, CODEN: JAFCAU ISSN: 0021-8561. Journal written in English. CAN 135:343592 AN 2001:636476 CAPLUS

Abstract

A modeling method for the induction of resveratrol synthesis by UV irradn. pulses in Napoleon table grapes is proposed. The method is based on the combination of four main parameters: irradn. power (IW), irradn. time (IT), irradn. distance (ID), and no. of elapsed days to achieve the highest resveratrol accumulation (Dm). Maximum resveratrol content (11-fold higher than untreated grapes) was achieved using the combination: IW = 510 W, IT = 30 s, ID = 40 cm, and Dm = 3 days. Sensory characteristics and main features of irradiated grapes (color, wt., firmness, flavor, size, ripening index and vitamin C content) remained unaltered after 1 wk of storage. The UV induction signal migrated to the hidden side of the grape skin with a delay of 3 days as compared to the directly irradiated side. Phenolic compds. were not detected in Napoleon grape flesh. Resveratrol content per std. serving (200 g) of irradiated grape was about 3 mg, an amt. more than 10-fold higher than that of untreated Napoleon grapes. This means that a serving of irradiated grape (unpeeled) could supply the resveratrol content equiv. to 3 glasses of a red wine with high resveratrol content (≈ 1 mg/glass). Therefore, controlled UV irradn. pulses are useful as a simple postharvest treatment (and alternative to genetic engineering) to obtain possible "functional" grapes (with enhanced health-promoting properties) as a dietary source of high resveratrol content.

Indexing -- Section 17-10 (Food and Feed Chemistry)
Section cross-reference(s): 8, 11

UV radiation
(resveratrol-enriched table grapes obtained by UV irradn.)

Grape
(table; resveratrol-enriched table grapes obtained by UV irradn.)

501-36-0, Resveratrol
Role: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(resveratrol-enriched table grapes obtained by UV irradn.)

Supplementary Terms

resveratrol enrichment grape UV radiation

Figure 22: Bibliographic information about "Postharvest Induction.... "of the authors of the invention" Postharvest treatment of fruit and vegetables...."
Source data and graphics: Sci-Finder Scholar (2006)

Documents cited in the scientific article and are considered significant in the investigation attached to the international PCT application are then picked.

C. DOCUMENTOS CONSIDERADOS RELEVANTES

Categoría *	Documentos citados, con indicación, si procede, de las partes relevantes	Relevante para las reivindicaciones nº
P, X	CANTOS, E. et al. "Postharvest induction modeling method using UV irradiation pulses for obtaining Resveratrol enriched table grapes: A new "funtional" fruit? ". Journal of Agricultural and Food Chemistry, octubre 2001. Vol. 49, nº 10, páginas 5052- 5058.	1 - 4
X	CANTOS, E. et al. "Effect of postharvest ultraviolet irradiation on Resveratrol and other phenolics of Cv. Napoleon table grapes". Journal of Agricultural and Food Chemistry, octubre 2000. Vol. 48, nº 10, páginas 4606-4612.	1 , 4
X	ADRIAN, M. et al. "Stilbene content of mature *Vitis vinifera* berries in response to UV-C elicitation". Journal of Agricultural and Food Chemistry, 2000.Vol. 48, nº 12, páginas 6103-6105.	1 , 4
X	NIGRO, F. et al. "Use of UV-C light to reduce *Botrytis* storage rot of table grapes" Postharvest Biology and Technology,1998. Vol. 13, nº 3, páginas 171-181.	1 , 4

☒ En la continuación del recuadro C se relacionan otros documentos ☐ Los documentos de familia de patentes se indican en el anexo

* Categorías especiales de documentos citados:

"A" documento que define el estado general de la técnica no considerado como particularmente relevante.

"E" solicitud de patente o patente anterior pero publicada en la fecha de presentación internacional o en fecha posterior.

"L" documento que puede plantear dudas sobre una reivindicación de prioridad o que se cita para determinar la fecha de publicación de otra cita o por una razón especial (como la indicada).

"O" documento que se refiere a una divulgación oral, a una utilización, a una exposición o a cualquier otro medio.

"P" documento publicado antes de la fecha de presentación internacional pero con posterioridad a la fecha de prioridad reivindicada.

"T" documento ulterior publicado con posterioridad a la fecha de presentación internacional o de prioridad que no pertenece al estado de la técnica pertinente pero que se cita por permitir la comprensión del principio o teoría que constituye la base de la invención.

"X" documento particularmente relevante; la invención reivindicada no puede considerarse nueva o que implique una actividad inventiva por referencia al documento aisladamente considerado.

"Y" documento particularmente relevante; la invención reivindicada no puede considerarse que implique una actividad inventiva cuando el documento se asocia a otro u otros documentos de la misma naturaleza, cuya combinación resulta evidente para un experto en la materia.

"&" documento que forma parte de la misma familia de patentes.

Figure 23: Fragment of the international research report indicating the documents considered significant invention of the international application (PCT) WO 02/085137 for the international extension of the Spanish patent ES-2177465

Source: WIPO (2002)

The national and international finance research centre Centro de edafología y biología aplicada (a group concerned with quality, safety and bioactivity of plant foods) affiliated with Council for Scientific Research, which have enabled the progress of a particular line of research that led to the invention.

Postharvest treatment of fruits and vegetables with ultraviolet light. Effect on phenolic metabolism and its relation to quality for fresh consumption and processing
Funding entity: CICYT During: 1997-2000 main researcher: F. Tomás-Barberán
Effect of processing technology on constituents of nutritional antioxidants in fruits and vegetables, Postharvest
Funding entity: CICYT During: 1998-2001 Main researcher: F. Ferreres
Increase of functional properties juices by enzymatic or physical treatments and the addition of ingredients rich in antioxidants and polyphenols available in nature
Funding entity: CICYT During: 2001-2004 Main researcher: F. Tomás-Barberán

Figure 24: Drivers of international research of CEBAS of CSIC
Source: http://www.cebas.csic.es/Departamentos/alimentos/proyec_calidad.htm

Study of the activation process of latent (lettuce) polyphenol oxidase
Funding entity: Comisión Europea Duration: 2000/2001 Main researcher: F.A. Tomás-Barberán
Study of phenolic composition of wines and Greens Rias Baixas and its relationship with ESCA
Funding entity: CSIC/ICCTI Duration: 2002/2003 Main researcher: F. Ferreres (CEBAS) y A. Dias (Univ. do Minho)
Flavonoids in fruits and vegetables: their impact on the quality of the food, nutrition and human health (Flav).
Funding entity: COMISIÓN EUROPEA Duration: 2004-2007 Main researchrs: Francisco A. Tomás-Barberán Other participants: María Isabel Gil; Juan Carlos Espín; Federico Ferreres

Figure 25: Drivers of international projects research CEBAS CSIC
Source: http://www.cebas.csic.es/Departamentos/alimentos/proyec_calidad.htm

Obtaining grape juice enriched with the natural anticancer compound resveratrol and the upgrading of products generated in production.
Funding entity: AGROVIDSA S.L. Duration: 2004-2006 Main researchers: Juan Carlos Espín de Gea Other participants: Francisco A. Tomás-Barberán, María Isabel Gil, Rocío González, Pilar Truchado
Scaling and adapting the patent 2 177 465 'post-harvest treatment of fruit and vegetables using pulses of ultraviolet irradiation.
Funding entity: ACTAFARMA S.L. Duration: 2005-2006 Main researcher: Juan Carlos Espín de Gea Other participants: Francisco A. Tomás-Barberán, Rocío González Barrio, Pilar Truchado

Figure 26: Contracts with firms: technology transfer CEBAS CSIC
Source: http://www.cebas.csic.es/Departamentos/alimentos/proyec_calidad.htm

7. Opportunities for the incorporation and development of technology for synthesis, processing and use of resveratrol

7.1. Expectations and real opportunities

With regard to opportunities for the incorporation and development of technology synthesis, technology transfer through licensing contracts[12] for the exploitation of the Spanish patent ES-2177465 from CEBAS (CSIC), new aspects have been established for the development and marketing:

- functional food[13] or nutraceuticals with Agrovidsa, sl, (based in Murcia) a company dedicated to the production of fruit juice and products derived from the surplus (skins, etc) once the grapes have been pressed to get the wine.
- OTC products (products without a pharmaceutical prescription, for the treatment of minor illnesses) with therapeutic innovations ActaFarma: One of the Spanish laboratories leading in exportation, importation and development of new products. There are laboratories for marketing through FDA group14 company

Functional food products or nutraceuticals are natural complements biocatius chemical compounds that can provide nutritional benefits in addition to the traditional nutrients they contain. They have the potential to strengthen disease prevention[15].

The functional food industry is highly regulated in Japan and the U.S. Nutraceuticals have a specific category in the field of health products. Since 1993 there has been a large number of these products developed for European markets. Until 2002 there was no specific regulation and the market was under the label of "food supplements".

Food law in Europe, as established on January 28, 2002, under which professionals from the food industries in Europe had two years to align their processes and activities to the new requirements. This regulation (OPTI_VT, 2002) sets out obligations for the application in the food industries, among others on the market and food traceability. In the European Union is reviewing the proposal to Parliament and the Council on nutrition and health foods in July 2003.[16]

[12] The technological transfer consists of "A change in ownership of rights (intellectual property of a set of information and expertise), but not necessarily imply a change in ownership, but often provides only the possibility of holding ". The license, an example of technology transfer, is defined as one "contract whereby the holder of a patent or know-how (licensing) allows a third party (licensee) to exercise certain powers to exploit the same. Comparable to renting " (Vidal-Quadras, 2005).

[13] "On this issue, the most widely accepted definition of functional food is a food looks similar to a conventional food, consumed as it is apart from a normal diet and beyond their usual nutritional contribution has proven scientifically to have physiological benefits and / or help reduce the risk of contracting a certain disease." (Buesa, Echarri y Torrecilla, 2005).

[14] Description from the ActaFarma website: www.actafarma.com

[15] Definition drawn from www.nutraceuticos.com and www.websalud.com

[16] COM (2003) 424 final. 2003/0165 (COD), cited in report on functional foods: http://www.ruralcat.net/ruralcatNews/resources/303653_alimentos_funcionanles.pdf.

Figure 27: Capture website product 'resveratrol' catalogue 'Supersmart' European company selling nutritional supplements

Source: www.supersmart.com

7.2. Expectations and opportunities

A good example of the variety of perspectives and opportunities associated with the field of food and pharmaceuticals, we can detect the contents of contracts with other companies to transfer technology CEBAS CSIC for product development

.

CONTRACTS WITH COMPANIES
Characterization of bioactive compounds in varieties of broccoli and tomato, Seminis.
Funding entity: Seminis Vegetables Seeds Inc. Duration: 2004- 2005. Main researcher: Francisco A. Tomás-Barberán. Other participants: Alicia Marín
FRUTIBON (San Juan, Alicante) Contract of transferring technology.
Funding entity: FRUTIBON Duration: 2004-2006 Main Researcher: María Isabel Gil Muñoz Other participants: María Angeles Conesa, Mercedes Almagro
HONGOS DEL DIA (Vega Mayor y Ayecue). Contract of transferring technology.
Funding entity: Hongos del Día (Florette y Ayecue) (Milagro, Navarra e Iniesta) Duration: April 2005-November 2005. Main researcher: Maria Isabel Gil Muñoz Other particpants: Juan Antonio Tudela, Mercedes Almagro
Analytical methodology of cocoa polyphenols.

Funding entity: Natraceutical S.A. Duration: Mayo 2005-Octubre 2005. Main researcher: Francisco A. Tomás-Barberán. Other participants: Alicia Marín
Characterization of Flavonoid compounds of Seminis' tomato varieties'
Funding entity: Seminis Vegetables Seeds Inc. Duration: 2005- 2006. Main researcher: Francisco A. Tomás-Barberán. Other participants: Begoña Buendía, M.I. Gil; J.C. Espín; F. Ferreres.
Characterisation of bioactive compounds of Seminis' sweet pepper genotypes
Funding entity: Seminis Vegetables Seeds Inc. Duration: 2005- 2006. Main researcher: Francisco A. Tomás-Barberán. Other participants: Begoña Buendía, M.I. Gil; J.C. Espín; F. Ferreres.
Scaling and adapting the patent 200002073 'synthesis of antioxidant enzyme hidroxitirosol.
Funding entity: ROVI Laboratorios Farmaceúticos S.A. Duration: 2005-2006 Main researcher: Juan Carlos Espín de Gea Other participants: Francisco A. Tomás-Barberán, Mar Larrosa Pérez.
'Study on strength and determination of cocoa polyphenols'
Funding entity: Natraceutical S.A. Duration: 2005-2006 Main researcher: Francisco A. Tomás-Barberán.
'Bioavailability of flavonoids in cocoa mixed with enriched ingredient Natraceutical ME521101'
Funding entity: Natraceutical S.A. Duration: 2005-2006 Main researcher: Francisco A. Tomás-Barberán

Figure 28: Other contracts with Companies about the transference of technology of CEBAS del CSIC Source: http://www.cebas.csic.es/Departamentos/alimentos/proyec_calidad.htm

Technology transfer for adaptation of the patent 200002073 'synthesis of antioxidant enzyme hidroxitirosol' to pharmaceutical ROVI.

In this example to determine the expectations and opportunities, the specialist researcher should calibrate the relationship of these developments with the lines of investigation. The prevention and treatment of venous thromboembolic disease, the use of Bemiparina haemodialysis, or in the production of suppositories, or incorporation of future developments.

8. Conclusion

As for the analysis of the scientific and patent throughout this article, we evaluated the actual outcome of different types of indicators according to their means.

In this regard we have confirmed as quantitative indicators, technical or related technology to certain key terms or uses. These quantitative indicators consist of a simple computer publications around us may indicate a dynamic field of science or the relationship between patents and scientific output.

Qualitative indicators work from the information contained in the records of a scientific paper or a patent, or from the relationship between citations in the case of scientific production. Qualitative indicators can facilitate thematic classification or the origin of scientific output and patents. However calculations that consider these quality characteristics can only get visions general indicators and in some cases are distorted.

The patent literature is an example of information that is resistant to quantitative analysis, if the aim is to avoid getting into the contents of the documents. There are differences in the strategies adopted by companies and legislation regarding the registering of patents in different counties. Information systems of patent databases in relation to information and communication ensure that the particular company / applicant and/or inventor have the difficult task of preparing, cleaning and processing of data for analysis.

The dataset features from casuistic and heterogeneous particulars. For example, for exact identification of the actors, dates and availability of inventions, one must know what's in the U.S.
It must be patented by the inventor. Patent rights are determined by the date of invention, not the date of the application, which only be issued by the applicant himself.

Qualitative indicators will to classify roughly the thematic lines of inquiry from the subject of documentary records using key terms. However the thematic codes of the CIP (International Patent Classification) that describe the invention in the U.S. also need to be looked at. They are assigned by automated translation of the codes of the classification itself, which is a source of errors.

Qualitative indicators also called relational indicators of the 1st generation (Callon, Courtial and Penan, 1995), for example, the method of joint appointments. These calculations, when we want to extend the patent literature with topic reference or practice, are not a well-established encryption and are an unreliable tool.

Ultimately, the use of these calculations in patent literature for thematic indirect classification, or for the identification and grouping of the actors is an unsound tool and only provides a rough picture

Scientific research and technology innovation is in the production of patents. Scientific research in this regard does not focus only on innovative products, but new procedures for obtaining goods or synthesis of new applications or utilities.

In scientometrics, relational indicators (second-generation relational according to Callon, Courtial and Penan) conform to the technical content in dealing with advanced methods such as analysis of associated words (co-word analysis) (Callon, Courtial and Penan, 1995). However, scientific research that supports the patent technically is not just about the component itself, resveratrol, but on the treatment of the product and the natural production that contains the summary procedure, the effect, the functional use and the final product result.

However, investigation of increasing concentrations of resveratrol, scientific research that supports the patent, technically is not just about the component itself, resveratrol, but about the treatment of the product and the natural production, the process of synthesis, the effect, the functional use and the final product. With this higher level and careful analysis of the scientific literature that supports the patent, we are not interested in information that may result from the calculations of the records associated with a use or a specific term. This is not just to consider the relationship between science and technology, based on qualitative indicators that work on scientific publications and citations from patents in order not to identify the interactions between scientific and technical fields, but also to structure content.

In order to draw the structure that describes the content of scientific research, we must realise when we are starting an investigation looking into a substitute for food or natural products that include them, on the procedures or treatments one might apply to obtain a certain effect or another, resulting in a functional use, and on what product is the depositary of the final invention (a drug, an additive, a functional food). We are now interested in the content of scientific research, including scientific publications and patents, using excerpts from articles on patents. In this sense we speak of those who agree the relational indicators relate to the content associated with science and technology.

The references that include reports on the state of the art and the description of the invention in the case of patents are not a result of systematic and quality, they are heterogeneous. History shows that the interests affected by allegations of infringement and other claims.

Therefore, one must read a summary of the documents in order to represent an approximation of the major relational classifications derived. In order to not repeat the content, the following selection of documents that describes much of the research associated with resveratrol under different parameters.

Finally, the development of a relationship diagram (Figure 14.18) that represents the connection between the parameters that define the research on resveratrol, we could say the diversity of references could be measured in innovation processes. For example: a component of a particular food, linked to a procedure or treatment, and a functional use, and so on.

With regard to opportunities for the incorporation and development of technology synthesis, technology transfer through licensing contracts for the exploitation of the Spanish patent ES-2177465 from CEBAS (CSIC), new aspects have been established for the development and marketing, that have been established for the development and marketing of functional foods or nutraceuticals and OTC products (products without a pharmaceutical prescription, for the treatment of minor illnesses)

A good example of the variety of perspectives and opportunities associated with the field of food and pharmaceuticals, we can detect the contents of contracts with other companies to transfer technology CEBAS CSIC for product development