

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO	
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DEP: 2020 DIRECCION DE NUEVAS CREACIONES	EVE: 1 REGISTRO/DEPOSITO/CONCESION/DEPOSITO
TRA: 2 PATENTES DE INVENCION	FOLIOS: 5
ACT: 519 PRESENTACION	

DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado(a)/Señor(a)
ANDRÉS MÁRQUEZ ACOSTA

Asunto: Radicación: 12-49718- -4
 Trámite: 2
 Evento: 1
 Actuación: 519
 Oficio: 4266
 Folios: 5

Patente de Invención	X			Patente de Modelo de Utilidad	
Vía Nacional	X				
Vía PCT (Fase Nacional)		Capítulo I		Capítulo II	
No. Solicitud Internacional					
Fecha de Presentación Internacional					

Como resultado del examen de fondo realizado, con fundamento en el Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

1. Documentos estudiados

Descripción:	Rad. N° 12-049718-00000-0000	23/Marzo/2012
Reivindicaciones:	Rad. N° 12-049718-00000-0000	23/Marzo/2012

2. Objeto de la invención

De acuerdo con lo establecido en el numeral 1.2.2.2 del capítulo primero del Título 10 de la Circular Única para efectos del examen de patentabilidad, se tendrá en cuenta la tasa pagada por el solicitante al momento de comenzar el examen para las reivindicaciones adicionales; esto es que cuando la solicitud contenga más de diez (10) reivindicaciones y no se haya pagado la tasa complementaria, sólo se estudiarán las cubiertas por la tasa pagada. En el

presente caso se estudiará la totalidad del capítulo reivindicatorio (reivindicaciones 1-7).

Título de la solicitud: “COMPOSICIÓN EN GEL PARA EL TRATAMIENTO O PREVENCIÓN DE MASTITIS EN MAMÍFEROS, LA CUAL SE BASA EN EL USO DE COMPONENTES NATURALES Y ALOE VERA”.

El problema planteado en esta solicitud consiste en la necesidad de suministrar una composición, de origen natural, adecuada para prevenir o curar la mastitis en mamíferos.

Para resolver este problema técnico la solicitud en estudio proporciona una composición según Rad. N° 12-049718-00000-0000.

3. De la solicitud de patente

Titulo

El título no debe incluir expresiones que mencionen o que tengan que ver con un “tratamiento” terapéutico.

Reivindicaciones (Art 30 D 486, Art 22 PCT)

La reivindicaciones 1 no debe incluir la expresión “para el tratamiento y/o prevención de mastitis en mamíferos”, además no se puede afirmar que la composición contiene componentes 100% naturales, porque acorde a lo divulgado en la descripción, la composición puede además comprender un antibiótico preferiblemente de origen natural, lo cual no descarta cualquier otro antibiótico obtenido sintéticamente.

La reivindicación 5 menciona que además comprende un antibiótico preferiblemente de origen natural, lo cual no descarta cualquier otro antibiótico obtenido sintéticamente, como se soporta en la descripción, de manera que no se puede afirmar que la composición contiene componentes 100% naturales.

La reivindicación 6, no es concisa porque la expresión “componentes aromáticos” no define ningún tipo de compuesto en específico.

4. Determinación del Estado de la Técnica

El estado de la técnica se determinó con base en la fecha de presentación de la solicitud de patente nacional: marzo 23 de 2012, y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Ítem	Documento	Título	Fecha de Publicación*
D1	US6869624	Product and process for stabiizing aloe vera gel	Marzo 22 de 2005

D1 divulga el proceso de obtención del gel de aloe vera el cual es estabilizado con componentes como ácido ascórbico y benzoato de sodio, además puede comprender ácido rosmarínico.

5. Examen de Patentabilidad (Art 14 D486)

Novedad (Art 16 D486)

La reivindicación 1 consiste en una composición según Rad. N° 12-049718-00000-0000.

Comparación de las características técnicas esenciales, con las del estado de la técnica:

Características esenciales	D1
Aloe Vera	Aloe Vera
Vitamina C	Vitamina C
Benzoato de sodio	Benzoato de sodio

Las características esenciales de la composición de la reivindicación 1 habían sido divulgadas previamente en el documento D1, el cual enseña, un gel de aloe vera estabilizado con ácido ascórbico y benzoato de sodio (ejemplos col. 6, tratamiento E, y tratamiento H).

En consecuencia, la reivindicación 1 no es nueva, según lo divulgado en el documento D1.

Nivel inventivo (Art18 D486)

La reivindicación 2 consiste en una composición según Rad. N° 12-049718-00000-0000.

Comparación de las características técnicas esenciales, con las del estado de la técnica:

Características esenciales	D1
Composición que comprende:	Obtención de gel de aloe vera que comprende:
Aloe Vera 70-99%	Aloe Vera 95.5%-99.8%
Vitamina C 0.5%	Vitamina C 0.5%
Benzoato de sodio 0.5%	Benzoato de sodio 0.05% -0.5%

Los documentos D1 se considera el estado de la técnica cercano a la invención definida en la reivindicación 1 porque D1 divulga el gel de aloe vera el cual se puede estabilizar con ácido ascórbico al 0.5% (col.6, ln 21), benzoato de sodio (0.5%, col. 5, ln 0.05% a 0.5%) entre otros, también menciona que incluye el ácido rosmarínico conocido por sus propiedades antiinflamatorias y antibacteriales¹, en cantidad de 0.01% y 0.5% en peso de gel de aloe vera (col. 2, ln 30-31); asimismo divulga que el gel de aloe vera es utilizado, tradicionalmente, como un antiinflamatorio tópico para combatir la inflamación causada por picaduras de insectos o quemaduras solares y similares (col. 1, ln-27-30). Dicho documento divulga tratamientos estabilizantes de gel de aloe vera (ej. 1, col. 6) en donde los tratamientos contienen las siguientes proporciones de agentes estabilizantes B, C, D (0.2%), A (0.5%), G (0.6%), F (1.7%) y H (4.5%) de manera que el resto corresponde a gel de aloe vera en proporciones de 99.8%-95.5%

1 Rosmarinic acid Phytochemistry 62(2003)121-125. Maike Petersen, Monique S.J. Simmonds
Adjunto a concepto.

La diferencia entre la invención, definida en la reivindicación 1, y el gel estabilizado de D1 consiste en que la anterioridad no enseña el porcentaje específico 0.5% de benzoato de sodio en los tratamientos del ejemplo 1.

No obstante esta diferencia no es posible evidenciar un efecto sorprendente.

Por lo tanto, el problema técnico objetivo que pretende resolver esta invención se puede formular así: “cómo modificar el gel de D1, para obtener otro gel alternativo de aloe vera con la misma actividad”.

Además es importante mencionar que el gel de aloe vera es ampliamente conocido por sus propiedades y beneficios como cicatrizante, antiinflamatorio, antiséptico entre otras².

Asimismo, se observa que la descripción menciona como modalidad preferida la composición que comprende 99% de aloe vera y adicionalmente cabe señalar que los resultados divulgados en el ejemplo de la descripción no permiten evidenciar un efecto sorprendente porque lo que se concluye es que el gel reivindicado presentó un efecto antibacterial, efecto o propiedad que ya es conocido en el arte previo para el aloe vera (referencia 2).

Sin embargo, la utilización de agentes estabilizantes para aumentar la vida útil del gel ya está divulgada en el documento D1.

En consecuencia, la persona del oficio normalmente versada en la materia, incluiría las proporciones de agentes estabilizantes mencionadas en D1, en el gel obtenido con el procedimiento ahí citado, para llegar así al objeto de la reivindicación 1 de la solicitud. Por lo cual se considera obvia. Las reivindicaciones dependientes 2-7, no mencionan alguna característica que haga inventiva a la composición de la reivindicación 1, por lo cual se considera que no son inventivas.

6. Conclusión

Los requisitos de Patentabilidad de la presente solicitud están afectados así:

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	US6869624	1 /2-7	Novedad /Nivel inventivo

²https://web.archive.org/web/20130603131644/http://www.cristaldesabila.com/beneficios_del_aloe/index.php

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir del día siguiente de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Se invita al solicitante se sirva indicar, si así lo considera, su renuncia al término faltante de sesenta (60) días para dar respuesta a este requerimiento y presentarla por escrito.

Finalmente, se le recuerda al solicitante que si como respuesta a este requerimiento llegara a modificar el capítulo reivindicatorio y éste contenga más de diez (10) reivindicaciones, no pagará la tasa de modificación voluntaria pero sí la correspondiente al pago por reivindicación adicional.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.



JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista, de fecha 2014-04-08

Elaboró: Lyna Del Carmen Mordecay Dunoyer
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Molecules of Interest

Rosmarinic acid

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Abstract

Rosmarinic acid is an ester of caffeic acid and 3,4-dihydroxyphenyllactic acid. It is commonly found in species of the Boraginaceae and the subfamily Nepetoideae of the Lamiaceae. However, it is also found in species of other higher plant families and in some fern and hornwort species. Rosmarinic acid has a number of interesting biological activities, e.g. antiviral, antibacterial, antiinflammatory and antioxidant. The presence of rosmarinic acid in medicinal plants, herbs and spices has beneficial and health promoting effects. In plants, rosmarinic acid is supposed to act as a preformed constitutively accumulated defence compound. The biosynthesis of rosmarinic acid starts with the amino acids L-phenylalanine and L-tyrosine. All eight enzymes involved in the biosynthesis are known and characterised and cDNAs of several of the involved genes have been isolated. Plant cell cultures, e.g. from *Coleus blumei* or *Salvia officinalis*, accumulate rosmarinic acid in amounts much higher than in the plant itself (up to 36% of the cell dry weight). For this reason a biotechnological production of rosmarinic acid with plant cell cultures has been proposed.

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Keywords: Antioxidant; Boraginaceae; Caffeic acid esters; Lamiaceae; Plant cell cultures; Rosmarinic acid

1. Discovery of rosmarinic acid

Even before the chemical structure of rosmarinic acid (Fig. 1) was elucidated, rosmarinic acid and similar compounds have been known as “Labiatergerbstoffe”, a type of tannin known from species of the families Lamiaceae. The tannin-like compound from *Melissa officinalis* was described to be neither a condensed catechin nor a gallo- or ellagitannin, but probably containing caffeic acid. Shortly after, two Italian chemists, Scarpati and Oriente (1958), isolated for the first time rosmarinic acid as a pure compound and named the compound rosmarinic acid according to the plant it was isolated from, *Rosmarinus officinalis*. The structure was elucidated as an ester of caffeic acid and 3,4-dihydroxyphenyllactic acid (Scarpati and Oriente, 1958). Biogenetic studies started in 1970 when Ellis and Towers fed radioactively labelled amino acids to *Mentha* plants and showed that the two aromatic amino acids phenylalanine and tyrosine are incorporated into rosmarinic acid. Interestingly, the caffeic acid part is only formed from

phenylalanine and the 3,4-dihydroxyphenyllactic acid part only from tyrosine (Ellis and Towers, 1970). These results were verified by similar feeding experiments with cell cultures of *Coleus blumei* (Razzaque and Ellis, 1977).

2. Derivatives of rosmarinic acid

A number of derivatives of rosmarinic acid (e.g. isorosmarinic acid = 3'-deoxyrosmarinic acid, Satake et al., 1999) as well as natural products containing one or two rosmarinic acid plus other aromatic moieties have been identified from higher plants (see Fig. 1 for examples). To name all these would go beyond the scope of this article. The best known rosmarinic acid derivatives may be lithospermic acid, a conjugate of rosmarinic acid and caffeic acid, and lithospermic acid B, a dimer of rosmarinic acid (Kelley et al., 1975; Tanaka et al., 1989).

3. Distribution of rosmarinic acid in the plant kingdom

Rosmarinic acid occurs throughout the Boraginaceae, whereas within the Lamiaceae it is restricted to the subfamily Nepetoideae (Litvinenko et al., 1975). Rosmarinic

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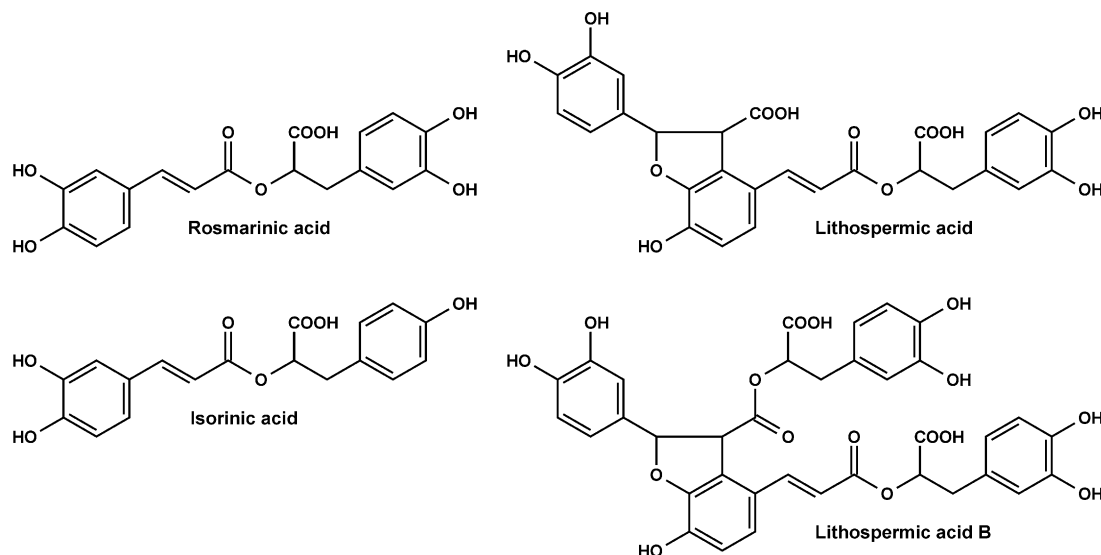


Fig. 1. Structures of rosmarinic acid and some derivatives.

acid has also been described from other plant families (Table 1). For example, it occurs in ferns of the family Blechnaceae (Häusler et al., 1992 and literature cited therein), lower plants such as the hornworts (Takeda et al., 1990) and in monocotyledonous plants like the sea grass family Zosteraceae (Ravn et al., 1994; Petersen, unpublished results), the related Potamogetonaceae (Petersen, unpublished results) as well as the Cannaceae (Simmonds et al., submitted). This distribution shows that the occurrence of rosmarinic acid cannot be used as a chemotaxonomical marker to differentiate among families. The question remains open as to whether the ability to synthesize and/or accumulate rosmarinic acid

has evolved rather early in the phylogeny of land plants or whether it has been developed independently in several taxa.

4. Chemical synthesis and biosynthesis of rosmarinic acid

Chemical synthesis of rosmarinic acid was long sought after and was finally achieved in 1991 by Albrecht (Zinsmeister et al., 1991). Since then a number of chemical syntheses of rosmarinic acid and derivatives, e.g. the methyl ester, different stereoisomers or the less hydroxylated isorosmarinic acid (Matsuno et al., 2002 and literature cited), have been described.

The enzymes involved in the biosynthesis of rosmarinic acid from its amino acid precursors have been unravelled in suspension cultures of *Anchusa officinalis* (Boraginaceae) and *Coleus blumei* (Lamiaceae) (see Fig. 2; Petersen et al., 1993; Petersen, 1997 and literature cited therein). Phenylalanine is transformed to an activated hydroxycinnamic acid by the enzymes of the general phenylpropanoid pathway which are already known from other biosyntheses, e.g. flavonoid or lignin biosynthesis. The first step is the deamination of L-phenylalanine to *t*-cinnamic acid by phenylalanine ammonia-lyase (PAL; E.C. 4.3.1.5). A PAL activity occurring coordinately with rosmarinic acid accumulation was for the first time shown by Razzaque and Ellis (1977). Basic characteristics of this enzyme were determined in protein preparations from a suspension cell line of *Coleus blumei* (Petersen et al., 1994). This cell line had the property to accumulate up to 21% of the dry weight as rosmarinic acid in only 10 days of cultivation when grown in a B5-based medium with high sucrose concentration (Ulbrich et al., 1985; Petersen et al., 1994). The reaction following the formation of *t*-cinnamic acid

Table 1
Examples for the occurrence of rosmarinic acid in the plant kingdom

Family	Reference
<i>Dicotyledonae</i>	
Lamiaceae	Scarpati and Oriente, 1958; Litvinenko et al., 1975
Boraginaceae	Kelley et al., 1975
Apiaceae	Hiller, 1965
Araliaceae	Trute and Nahrstedt, 1996
Cucurbitaceae	De Tommasi et al., 1991
Hydrophyllaceae	Petersen, unpublished results
Rubiaceae	Aquino et al., 1990
Plantaginaceae	Kurkin et al., 1988 cited in Holzmannova, 1995
Sterculiaceae	Satake et al., 1999
Tiliaceae	Lasure et al., 1994
<i>Monocotyledonae</i>	
Cannaceae	Simmonds et al., submitted
Zosteraceae	Ravn et al., 1994
Potamogetonaceae	Petersen, unpublished results
<i>Pteridopsida</i>	
Blechnaceae	Häusler et al., 1992
<i>Anthocerotopsida</i>	
Anthocerotaceae	Takeda et al., 1990

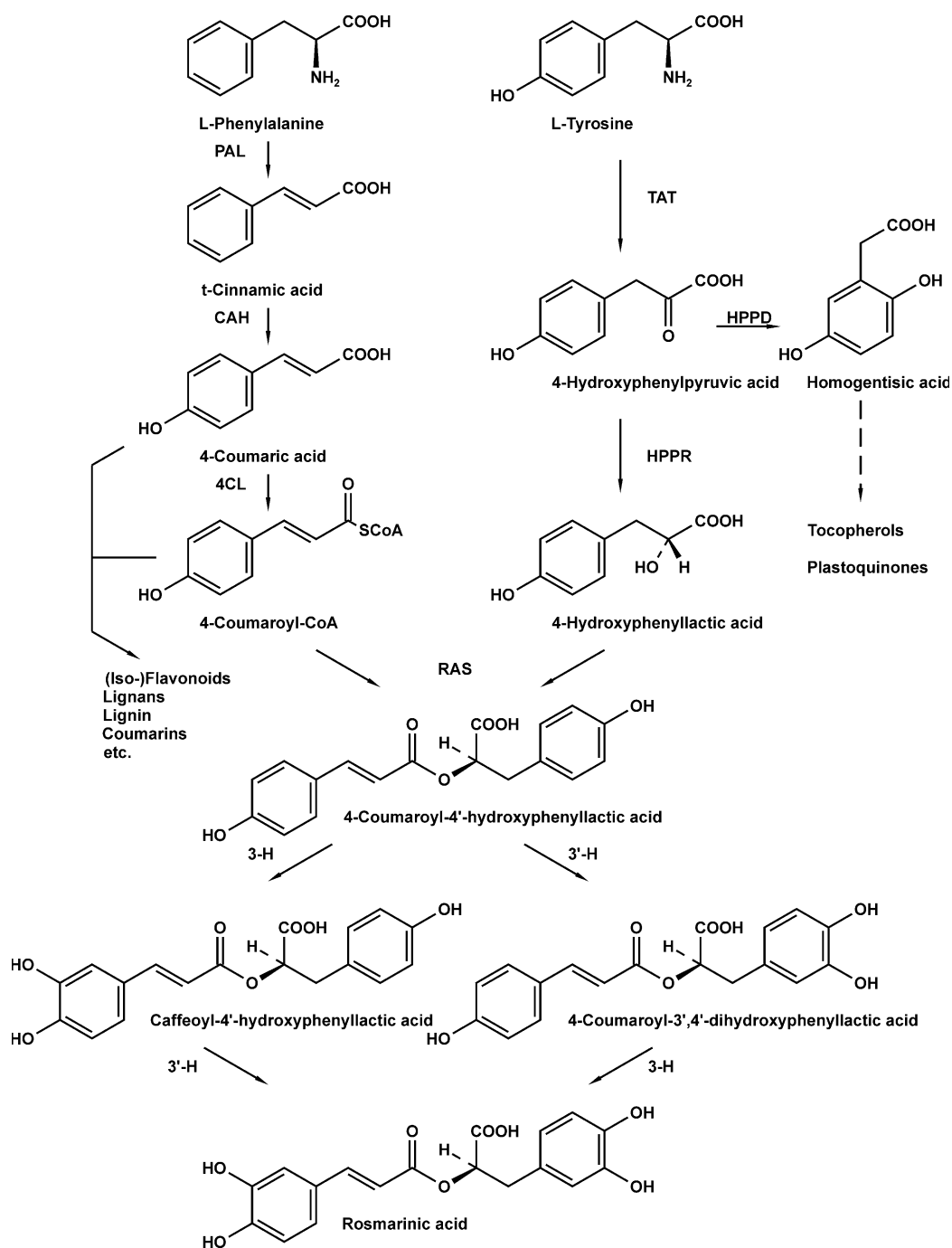


Fig. 2. Biosynthetic pathway for rosmarinic acid as found in suspension cultures of *Coleus blumei*. PAL=phenylalanine ammonia-lyase, CAH = cinnamic acid 4-hydroxylase, 4CL=hydroxycinnamate:coenzyme A ligase, TAT=tyrosine aminotransferase, HPPR = hydroxyphenylpyruvate reductase, HPPD=hydroxyphenylpyruvate dioxygenase, RAS=hydroxycinnamoyl-CoA:hydroxyphenyllactate hydroxycinnamoyl transferase, 3-H, 3'-H=hydroxycinnamoyl-hydroxyphenyllactate 3- and 3'-hydroxylases.

is its hydroxylation in position 4 to 4-coumaric acid by the cytochrome P450 monooxygenase cinnamate 4-hydroxylase (CAH; E.C. 1.14.13.11) which was also characterized from suspension cells of *Coleus blumei* (Petersen, 1997). It is generally accepted that hydroxycinnamic acids have to be activated before further reactions can take place. Several activation forms have been described. In most cases a coenzyme A thioester is

formed, but also glucose esters or other cinnamic acid esters, e.g. chlorogenic acid have been shown to be able to serve as donors of hydroxycinnamic acid moieties. In *Coleus blumei*, a hydroxycinnamate:coenzyme A ligase (4CL; E.C. 6.2.1.12) involved in the biosynthesis of rosmarinic acid was characterized. The other precursor for the ester formation is formed from tyrosine. The first step is the transamination of L-tyrosine with

2-oxoglutarate as second substrate to 4-hydroxyphenylpyruvate and glutamate by the pyridoxalphosphate-dependent transaminase tyrosine aminotransferase (TAT; E.C. 2.6.1.5) (De Eknankul and Ellis, 1987). A cDNA encoding TAT from *Coleus blumei* (EMBL GenBank Accession number AJ458993) was isolated and functionally expressed in *E. coli* recently (Lahrmann and Petersen, unpublished results). Since 4-hydroxyphenylpyruvate is not an intermediate of aromatic amino acid biosynthesis in plants, it has to be formed from tyrosine as described above. In addition to rosmarinic acid biosynthesis it serves as precursor for homogentisic acid, a precursor for the essential metabolites tocopherols and plastoquinones. The cDNA encoding hydroxyphenylpyruvate dioxygenase (HPPD; E.C. 1.13.11.27) involved in the formation of homogentisic acid has been isolated from *Coleus blumei* (EMBL GenBank Accession number AJ309203; Kim, 2002). For rosmarinic acid biosynthesis, 4-hydroxyphenylpyruvate is reduced to the corresponding 4-hydroxyphenyllactate by hydroxyphenylpyruvate reductase (HPPR; E.C. 1.1.1.237; Petersen et al., 1993). The enzyme accepts NADH as well as NADPH as co-substrates and also reduces 3,4-dihydroxyphenylpyruvate although with a lower affinity. A full-length cDNA for HPPR was recently isolated from *Coleus blumei* (EMBL GenBank Accession number AJ507733) and functionally expressed in *E. coli* (Kim, 2002). The resulting hydroxyphenyllactate is the *R*(+)-stereoisomer, and this is the only isomer accepted by the ester-forming enzyme hydroxycinnamoyl-CoA:hydroxyphenyllactate hydroxycinnamoyl transferase (trivial name: rosmarinic acid synthase (RAS; E.C. 2.3.1.140); Petersen et al., 1993). Under release of coenzyme A the ester linkage is formed between the carboxyl group of 4-coumaric acid and the aliphatic hydroxyl group of 4-hydroxyphenyllactate. The resulting ester is 4-coumaroyl-4'-hydroxyphenyllactate which is afterwards hydroxylated in positions 3 and 3' of the aromatic rings by two cytochrome P450 monooxygenases (Petersen, 1997). A cDNA for a cytochrome P450 catalyzing the 3-hydroxylation of the 4-coumaric acid part of the ester to a caffeic acid part was recently isolated from *Lithospermum erythrorhizon* (CYP98A6; Matsuno et al., 2002). A number of cDNAs encoding cytochrome P450s that are able to hydroxylate 4-coumaric acid or a 4-coumaroyl-moiety in an ester (e.g. 4-coumaroyl-shikimate) have been published recently (Schoch et al., 2001; Franke et al., 2002; Anterola et al., 2002). These cytochrome P450s are all grouped into the CYP98 family. A CYP98A14 with certain homology to the published sequences (see above) has been isolated from rosmarinic acid-synthesising suspension cells of *Coleus blumei* (EMBL accession number AJ427452; Petersen, unpublished result).

5. Biotechnological production of rosmarinic acid by plant in vitro cultures

Rosmarinic acid is readily accumulated in undifferentiated plant cell cultures, in some cases in concentrations much higher than in the plant itself. The first plant cell cultures accumulating rosmarinic acid were derived from *Coleus blumei* (Razzaque and Ellis, 1977; Zenk et al., 1977). Suspension cultures from this species were the first ones used for an attempted biotechnological production of rosmarinic acid since they were found to accumulate up to 21% rosmarinic acid in the dry weight. Ulbrich et al. (1985) reported on the isolation of about 100 g crystalline rosmarinic acid from suspension cells cultivated in a two-stage process in bioreactors of 32 l working volume for 14 days. Cell cultures of other species of plants were then used for rosmarinic acid production. The highest content of rosmarinic acid at 36% of the cell dry weight was described by Hippolyte et al. (1992) in a suspension culture of *Salvia officinalis* in a low osmolarity medium with 5% sucrose.

The effect of increased sucrose concentrations on rosmarinic acid accumulation was elucidated by Gertlowski and Peterson (1993) in a suspension culture of *Coleus blumei*. The level of rosmarinic acid accumulation was shown to be dependent on the sucrose content, whereas the growth limitation (e.g. by a limiting supply of phosphate) determined the onset of rosmarinic acid accumulation. Several authors showed that rosmarinic acid accumulation can furthermore be enhanced by the addition of fungal elicitors (e.g. yeast extract, preparations from *Pythium aphanidermatum*) or methyl jasmonate (see Szabo et al., 1999 and literature cited therein). This suggests that rosmarinic acid could have a role in plants as a defence compound against pathogens and herbivores. In fact, recent research has shown that rosmarinic acid is a potent phagodeterrent against the tobacco hornworm, *Manduca sexta* (Simmonds et al., submitted). It deters these larvae from feeding but if eaten is not toxic. We could find no other information in the literature about the effect of rosmarinic acid on other herbivores.

6. Biological activity of rosmarinic acid

A multitude of biological activities have been described for rosmarinic acid and a comprehensive description would go beyond the scope of this article. Main activities are adstringent, antioxidative, anti-inflammatory, antimutagen, antibacterial and antiviral (e.g. Parnham and Kesselring, 1985). The latter activity is used in the therapy of *Herpes simplex* infections with rosmarinic acid-containing extracts of *Melissa officinalis*. The antiinflammatory properties are thought to be based on the inhibition of lipoxygenases and cyclooxygenases

and the interference of rosmarinic acid with the complement cascade (Parnham and Kesselring, 1985). Rosmarinic acid is rapidly eliminated from the blood circulation after intravenous administration ($t_{1/2}$ = 9 min) and shows a very low toxicity with a LD_{50} in mice of 561 mg kg^{-1} after intravenous application (Parnham and Kesselring, 1985). Phenolic compounds like rosmarinic acid can provide protection against cancer and rosmarinic acid contributes to the anti-oxidant activity of plants used in the cosmetic industry, such as *Rosmarinus officinalis* and *Sanicula europaea* (D'Amelio, 1999).

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