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Patent Analysis as a Tool for Research Planning: Case Study of Phytochemicals in Tea

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The availability and ready access to computerized patent databases makes it possible to discover trends and relationships in research. Not all research gets published in papers and a lot of information is made available to the public through patents, a detailed analysis of patents granted on a particular area of research can provide some missing information. By analysing the patents and studying the prior art, the research gaps can be identified and the research work to be taken up can be focused.

The main aim of the work presented in this paper is the application of patent analysis in research planning. For this purpose, tea, which has gained importance over the years for its medicinal properties, has been taken as a case study. Studying the synthesis and accumulation of catechins is the focus of research not only in India but also worldwide. Hence, a complete analysis of the patents granted on the work related to research on the steps of metabolic pathway of catechin was done and the results are presented in this paper. The analysis has been done using various criteria, like the patenting trend over the years, a comparison of the assignees playing a major role, a comparison of the technology used in different patents and the patenting activity across the groups.

Keywords: Patent analysis, tea phytochemicals, catechin biosynthesis pathway

Scientists in research institutions and academics are very often inundated with scientific literature published in peer reviewed journals, but this literature has poor objective information on the technological strategies being adopted by the commercial companies in their research laboratories. This is because of the fact that technologies during their development phase are often protected by proprietary secrecy and are least visible.

A systematic analysis of patents may provide some of the missing information. The use of patent information is often limited to reference while submitting patent applications, identifying the characteristics of a specific patent or occasionally reviewing similar patents. The organization's patent staff/patent agent often does this work, with some assistance from scientists, but only modest attention from strategic planners.

Patent information provides a unique planning resource for managing R & D projects. One potential use of patent trend data is in evaluating the technological importance of a particular concept, process or product and their improvements. Consequently, in managing an R & D programme, the progamme leaders should seriously consider how their approach compares with others in terms of uniqueness, cost effectiveness and market acceptance. Systematic examination of other's patents and their prior art can help in making this comparison.

Patent data can also be used to more carefully define the 'pacing' technical problems or subsystems in a complex development programme. Pacing problems are those areas where needed improvements control the rate of development for the whole technology. In fact, analyses of the technical subcategories of an area using patents may stimulate new technical solutions.

These activities can lead to a better awareness of creative ideas and improved effectiveness of creative ideas and R&D resource allocation. Picking the technological winners and avoiding the losers in the R&D process provide an overall competitive advantage.

Patents in tea were analysed to gain an understanding of the technical approaches taken by different research groups throughout the world doing research in the same area. This represents a technology-focused analysis since patents were selected because of their relevance to the technical area regardless of the assignees represented, although

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it does give an idea about the relative positions of different research organisations.

Tea Phytochemicals: A Case Study

For 3,000 years, before it became a social and recreational beverage, tea was used as a medicine. The tea plant, *Camellia sinensis*, is a powerhouse with an array of cancer-fighting phytochemicals (non-nutrient plant chemicals). The most promising of these is catechin, a tannin derivative that gives tea its astringency and is common to many plants such as grapes, berries, and ferns.

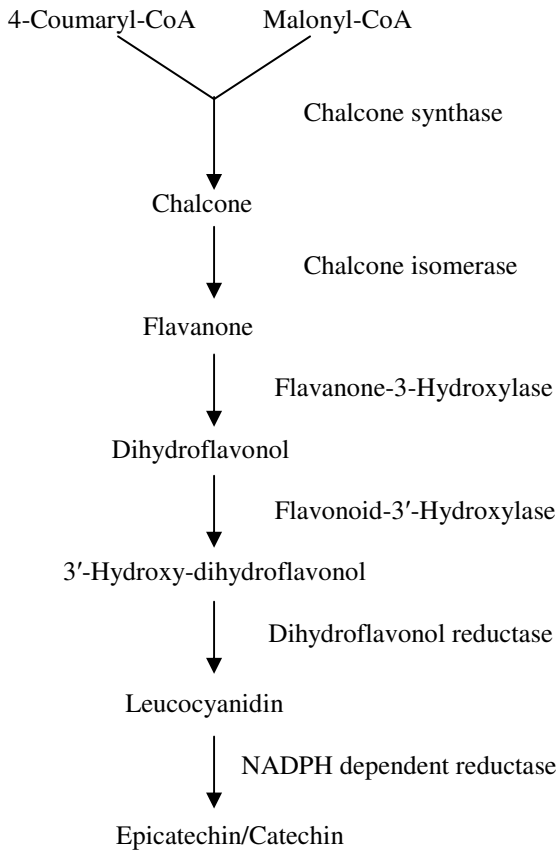
Catechins belong to the flavan-3-ol class of flavonoids. Green tea catechins are the flavan-3-ols found in green tea leaves (*Camellia sinensis*). The four major catechins in green tea leaves are: -epigallocatechin gallate (EGCG), -epicatechin gallate (ECG), -epigallocatechin (EGC) and (-)-epicatechin (EC). They are all polyphenolic substances.

Flavonoids are a class of water-soluble plant pigments. Flavonoids are broken down into categories, though the issue of how to divide them is not universally agreed upon. One system breaks flavonoids into isoflavones, anthocyanidins, flavans, flavonols, flavones, and flavanones. Flavonoids are found in a wide range of foods. For example, flavanones are in citrus, isoflavones in soy products, anthocyanidins in wine and bilberry, and flavans in apples and tea. The flavonoids are significant in their contribution to the colouration and other properties of higher plants. The functions of these pigments extend well beyond colouration of flowers, however. The pigments also colour fruits, leaves and other plant parts, and more importantly provide plants with UV protection, as well as protection against herbivores and microbes.

Flavonoid compounds present in tea not only contribute to flavour and astringency but also have an enormous medicinal value mainly because of their antioxidant properties. In the proposed research project, it is intended to clone the genes involved in catechin biosynthetic pathway and understand their regulation. The objective is to provide a technology package to transform the tea plant. Patents that are specific for cloning of the genes in tea plant to increase the content of catechin could not be traced. Therefore, it was decided to study the individual steps of catechin biosynthetic pathway and look for patents on those individual steps irrespective of the plant. This was based on the understanding that enzymes are the same in the flavonoid synthesis and there appeared to be some patenting activity by plant biotechnology companies to improve the pigmentation of flowers and fruits of plants, in general.

Catechin Biosynthesis Pathway

Important secondary metabolites such as catechins, epicatechins, anthocyanins, condensed tannins, isoflavonones are products of the flavonoid pathway. The crucial point in tea is the utilization of the pathway for the synthesis and accumulation of catechins in tender shoots. The pathway involves phenylalanine and acetyl CoA-derived precursors through a series of enzymes namely chalcone synthase, chalcone isomerase, flavanone-3-hydroxylase, flavonoid-3′-hydroxylase, flavonoid-3′,5′- hydroxylase, dihydroflavonol reductase and a few NADPH-dependent reductases belonging to a broad class of cytochromes P450s.



Major flavonoids in tea, known as catechins, are derived from phenylpropanoid pathway utilizing a series of enzymatic reactions.

The biosynthetic pathways of these various pigments have been extensively studied in many different plant species.

In order to study the prior art and different technical approaches taken in this field, a detailed patent search on all the intermediates and enzymes involved in the pathway was done.

The patents studied are on the cloning of genes which code for chalcone synthase, flavonol synthase, flavonoid 3′-hydroxylase, flavonoid 3′, 5′-hydroxylase, dihydroflavonol 4-reductase, glycosyltransferase. The products of the activity of these genes are intermediates in the final synthesis of catechins or epicatechin.

Patent Analysis

The patents granted for the flavonoid pathway engineering for tea have been analysed in order to get an idea about the patent status over the world. The patents have been classified in various groups based on the genes, which code for the enzymes mentioned in the group name and important keywords with respect to this study. Patent activity has been analysed with respect to the groups classified, the country wise comparisons and the activity over the years. The comparison of patent activity by assignees has also been examined. The simplest indication of patent activity is the total number of patents produced.

Technology Analysis

As mentioned above, the patents have been grouped according to the various enzymes and intermediates of the flavonoid pathway and the maximum focus of work in this area is on chalcone synthase. Most of the patents on the flavonoid pathway genes result in the improved means for altering colour patterns and colour intensity of flowers and other plant parts.

A—Catechin synthesis

The patents on catechin synthesis describe various methods for the synthesis of catechins. In one, a method for the identification of the gene of a desired phenotype, e.g. one desired phenotype is production of catechin and the said catechin is epigallocatechin gallate or epicatechin gallate. The presence of the phenotype in the cell cultures produced in response to a stimulus is determined[1]. The other method explains the production of catechin in a plant, *Wallichiana*, by tissue culture method[2]. There is one more patent on the isolation of catechin (proanthocyanidin) from *Vaccinium* culture. The culture is initiated for the production of proanthocyanidins, establishing a pigmented cell culture from the mentioned culture and then extracting the proanthocyanidins from the pigmented culture[3].

B—Chalcone synthase

The group including patents on chalcone synthase has been the principal area of research. The inventions describe the use of recombinant DNA technologies for genetically altering the plants. The transgenotes selected comprise a DNA segment operably linked to a promoter and a disabled Ti plasmid of *Agrobacterium tumefaciens* is used for the transformation. The recombinant nucleic acid comprises of a full length-coding region of a chalcone synthase gene segment[4]. There is an invention that describes a modified *Mazus* chalcone synthase (CHS) nucleic acids, which encode a modified chalcone synthase that has alanine instead of cysteine at the 165th amino acid of *Mazus* CHS and either glycine or lysine instead of methionine at the 138th amino acid of *Mazus* CHS[5]. The base sequences of novel chalcone synthase-like genes that can be used in breeding hop and as gene markers, and the amino acid sequences of proteins encoded by these genes are provided in one invention[6]. The genetically altering of *Petunia* plant by the introduction of antisense CHS cDNA by recombinant technology is the focus of one invention[7]. A new gene has been obtained from the petal of *Gentiana scabra* having a specific amino acid sequence, coding for a chalcone synthesizing enzyme for synthesizing pigments has also been given in one of the patents. A promoter of the gene for gentian chalcone synthase has been obtained. This is capable of inducing petal-specific expression of a foreign gene in plant[8]. There is one patent that describes a new chalcone synthase gene having specific base sequence involved in the anthocyanin synthesis[9]. The production of mutant polyketide synthase wherein the amino acids of chalcone synthase are substituted is one area of research in the patent[10]. A genetic system utilizing the light-regulated expression of the *Arabidopsis thaliana* chalcone synthase (CHS) gene is described in one patent[11].

C—Chalcone isomerase

The patents on chalcone isomerase describe various inventions. One of them describes the method of obtaining a DNA encoding an enzyme, especially

chalcone isomerase, related to the synthesis of a flower colour[12]. There is a method described in one of the patents for increasing the flavonoid content in tomato by treating it with a chalcone isomerase DNA[13]. There is an invention that relates to an isolated nucleic acid fragment encoding soybean enzymes that catalyze steps in biosynthesis of isoflavones, the enzyme is a member selected from the group consisting of chalcone isomerase, isoflavone reductase and vestitone reductase[14]. There is an invention that describes the modulation of condensed tannin production in plants. Here a transgenic plant is provided that is comprised of a transgenic coding sequence encoding a chalcone isomerase polypeptide[15]. The method of predicting the activity and/or substrate specificity of chalcone isomerase is one invention[16].

D—Flavonol synthase

There are not many patents on flavonol synthase. One patent describes the genetic sequences encoding the flavonol synthase enzyme of plant origin[17]. There is another patent that provides an isolated nucleic acid fragment encoding flavonol biosynthetic enzyme. The construction of a chimeric gene encoding all or portion of the flavonol synthase is described here[18].

E—Flavone synthase

The patents on flavone synthase are the recent ones. There are patents that aim at providing flavone synthase II genes with the activity of synthesizing flavones directly from flavanones. The introduction of the genes into plants can alter the flower colours of the plants. The DNA sequences are obtained from snapdragon or torenia[19]. A nucleic acid encoding flavone synthase I for preparing transgenic plants with altered flavone content is also patented[20].

F—Isoflavone biosynthesis

The patents on isoflavone biosynthesis are very few. There is an invention that pertains to nucleic acid fragments encoding enzymes involved in isoflavone biosynthesis in plants and seeds[21].

G—Isoflavonoid and flavonoid biosynthesis

There are many patents on isoflavonoid and flavonoid biosynthesis describing the production of flavonoids and isoflvaonoids in general. In one invention, the plants are genetically engineered for the production of isoflavonoids in legume roots and thus the nodulation efficiency is improved[22]. The methods for influencing the flavonoid biosynthetic activity in a plant cell have been disclosed in one invention[23]. There is an invention that relates to nucleic acids and nucleic acid fragments that encode amino acid sequences for flavonoid biosynthetic enzymes in plants and hence the modification of flavonoid biosynthesis is possible[24]. In one patent the method for altering the isoflavonoid profile in different parts of an isoflavonoid-producing plant has been disclosed[25]. A method for manipulating the production of flavonoids other than anthocyanins in plants by manipulating gene activity in the flavonoid biosynthetic pathway by expressing two or more genes encoding transcription factors for flavonoid biosynthesis, compositions for use in such a method and tomato plants having altered flavonoid levels are disclosed in one invention[26]. The method of increasing isoflavonoid production in isoflavonoid-producing plants by transforming the plants with a construct that regulates the expression of genes in the phenylpropanoid pathway is disclosed in one invention[27]. There is a patent on an invention that provides the use of a regulatory gene and encoded protein to alter the biosynthesis and accumulation of flavonoids including anthocyanins and condensed tannins in plants and plant tissues, particularly in alfalfa, white clover, and other forage legumes[28]. These patents, as a whole, describe various genes that are responsible for flavonoid and isoflavonoid synthesis.

H—Flavanone-3-hydroxylase

The patenting activity on flavanone-3-hydroxylase is limited and the patents describe the nucleic acid fragments that encode the flavanone-3-hydroxylase, the construction of a chimeric gene encoding the same and the expression of the chimeric gene results in production of altered levels of the enzyme in a transformed host cell [29].

I—Flavonoid 3', 5'- hydroxylase

There are quite a few patents on flavonoid 3′, 5′-hydroxylase . There is one patent that discloses the production of a transgenic plant capable of expressing a recombinant flavonoid 3′, 5′- hydroxylase that is capable of hydroxylating dihydrokaempferol [30]. There are patents on the invention that provides for transformation of plant cells with a recombinant DNA that encodes a polypeptide having flavonoid 3', 5'-hydroxylase activity. The transformed plant has a pigment pattern that it did not have originally [31].

J—Dihydroflavonol 4 – reductase

There is a good number of patents on dihydroflavonol 4 – reductase which describe the modified nucleic acid sequences that encode substrate-specific dihydroflavonol 4 – reductase (DFR). The modified DFR has an altered amino acid sequence at the substrate specificity-determining region. The DFR has the substrate specificity for dihydrokaempferol [32]. There are inventions that disclose the generation of transgenic plants exhibiting altered flower colour by the introduction of nucleotide sequence encoding DFR[33].

K—Anthocyanin Synthesis

In the group on anthocyanin synthesis, there is a patent on the nucleic acids that encode intermediates that lead to anthocyanin synthesis[34]. There are patents on the transgenic plants having altered anthocyanin levels. The enzymes encoded by these nucleic acids are involved in the anthocyanin synthesis from the flavonoid pathway[35]. There is an invention on the regulation of anthocyanin pigment production in *Petunia* [36]. There is an invention that provides a genetic sequence for encoding a polypeptide having plant anthocyanidin rutinoside aromatic acyl transferase activity [37].

L—Flavonoid Glycosylating Enzymes

The group on flavonoid glycosylating enzymes has a patent that describes the genetic sequences encoding flavonoid pathway metabolizing enzymes and, in particular, flavonoid glycosylating enzyme. The use of this invention is in manipulating production of pigment molecules in the plants[38].

M—Increasing Flavonoid Content

The patents on increasing flavonoid content are quite a few and describe the methods to increase the flavonoid content of plants by increasing the activity of various enzymes involved in the process. These patents disclose the genes that are responsible for the flavonoid pathway [39].

N—Flower Regulating Gene

The patents on the isolation of flower regulating gene include those on the production of a transgenic plant into which the gene is introduced [40].

O—Coumarate-3-Hydroxylase

The patent on coumarate-3-hydroxylase describes a method for altering secondary metabolism in plants, specifically phenylpropanoid metabolism. This invention is further directed to a mutant p-coumarate-3-hydroxylase gene[41].

P—Synthetic Methods

There are quite a few patents on various synthetic methods described for the production of catechins, polyphenols, chalcones and epicatechins[42].

Patenting Ativity across the Classified Groups

The table 1 gives the patenting activity in each group. It is observed that the group that contains patents on chalcone synthase has the maximum number of patents, followed by the group with patents on isoflavonoid and flavonoid biosynthesis and Dihydroflavonol-4-reductase. There is, howeve, only one patent that describes the identification of a gene that is responsible for catechin and epicatechin synthesis.

Table 1—Patenting activity across the groups

Group	No of patents	Group	No of patents
A	3	I	6
B	14	J	11
C	5	K	4
D	2	L	1
E	7	M	7
F	2	N	2
G	11	O	1
H	3	P	6

Patenting Activity over the Years

The Table 2 describes the patenting activity in this field over the years. It can be observed that the 2003 - 2004 has the maximum patenting activity. As such, the number of patents has increased since 1999 till 2004. In the years prior to 1999, there was very little activity. This indicates that the activity has been very recent and that this area has gained importance in the recent years.

Table 2—Patenting activity over the years

Year	No of patents
1989 - 1990	2
1991 - 1992	2
1993 - 1994	3
1995 - 1996	3
1997 - 1998	2
1999 - 2000	16
2001 - 2002	20
2003 - 2004	37

International Comparison

The patenting activity in different countries is given in table 3. It is observed that organizations from the United States of America have been the forerunners in obtaining patents, followed by Japan. Even Germany and Australia have been actively involved in the patenting activity. It can be observed that Italy and India have the least activity, with only one patent each. But overall it is seen that the patenting activity has taken place considerably worldwide with organizations from quite a few countries involved in it.

Table 3—Patenting activity in different countries

Country code	Country	No of patents
US	United States	16
JP	Japan	12
DE	Germany	11
AU	Australia	10
KR	Korea	6
GB	United Kingdom	4
NL	Netherlands	3
NZ	New Zealand	3
CA	Canada	2
FR	France	2
IT	Italy	1
IN	India	1

Comparison of Patenting Activity by the Major Assignees

The patent analysis in terms of level of activity gives a general understanding of the extent to which the firms are active in this area. The assignees that have US and non-US patents have been studied separately.

From the table 4, the following observations are made: (i) For US patents, International Flower Developments Pty Ltd has the maximum number of patents, followed by Du Pont, and (ii) For non US patents, Korea Kumho Petrochem Co Ltd has the maximum patents.

Tables comparing the patenting activity by the assignees in this field are given below.

Competitive Analysis

The firms active in the research related to tea phytochemicals are DNA Plant Technology Corporation, International Flower Development Pvt Ltd, E I Du Pont de Nemours & Co, Suntory Flowers Ltd and Korea Kumho Petrochemical Co Ltd.

DNA Plant Technology Corporation has concentrated on the development of transgenic plants using genes coding for flavonoid biosynthetic pathway enzymes, such as chalcone synthase, dihydroflavonol reductase. International Flower Development Pvt Ltd has done work on manipulating the production of pigmentory molecules in plants using genetic sequences encoding flavonol synthase enzyme, 3',5'-hydroxylase which is capable of hydroxylating dihydrokaempferol, flavonoid glycosylating enzyme and dihydroflavonol reductase. Du Pont has looked at the production of chimeric genes encoding flavonoid biosynthetic enzymes, especially genes that alter the level of expression of flavonol synthase. It has also got patents on enzymes involved in isoflavone synthesis, e.g. chalcone isomerase, isoflavone reductase and vestitone reductase. It has also developed nucleic acid fragments encoding flavanone3-hydroxylase in plants and seeds. Suntory Flowers Ltd work uses genetic engineering techniques for production of flavone synthase which controls flavone biosynthesis that affects the flower colour. Korea Kumho Petrochemical Co Ltd has produced genes that encode dihydroflavonol reductase with modified activity.

Patent Mapping

Figure 1 gives a patent map of all the US patents that are taken in this report. It can be seen from the map that US Pat No 5,034,323 is the principal patent. The forward citations are considered while making the patent map.

The invention in this patent relates generally to the use of recombinant DNA methods for genetically altering plants, and more particularly, to improved means for altering colour patterns and colour intensity of flowers and other plant parts. This patent describes the genetic engineering of novel plant phenotypes. It also describes a method for modifying colour pattern in a flower of a petunia plant having an endogenous chalcone synthase (CHS) gene.

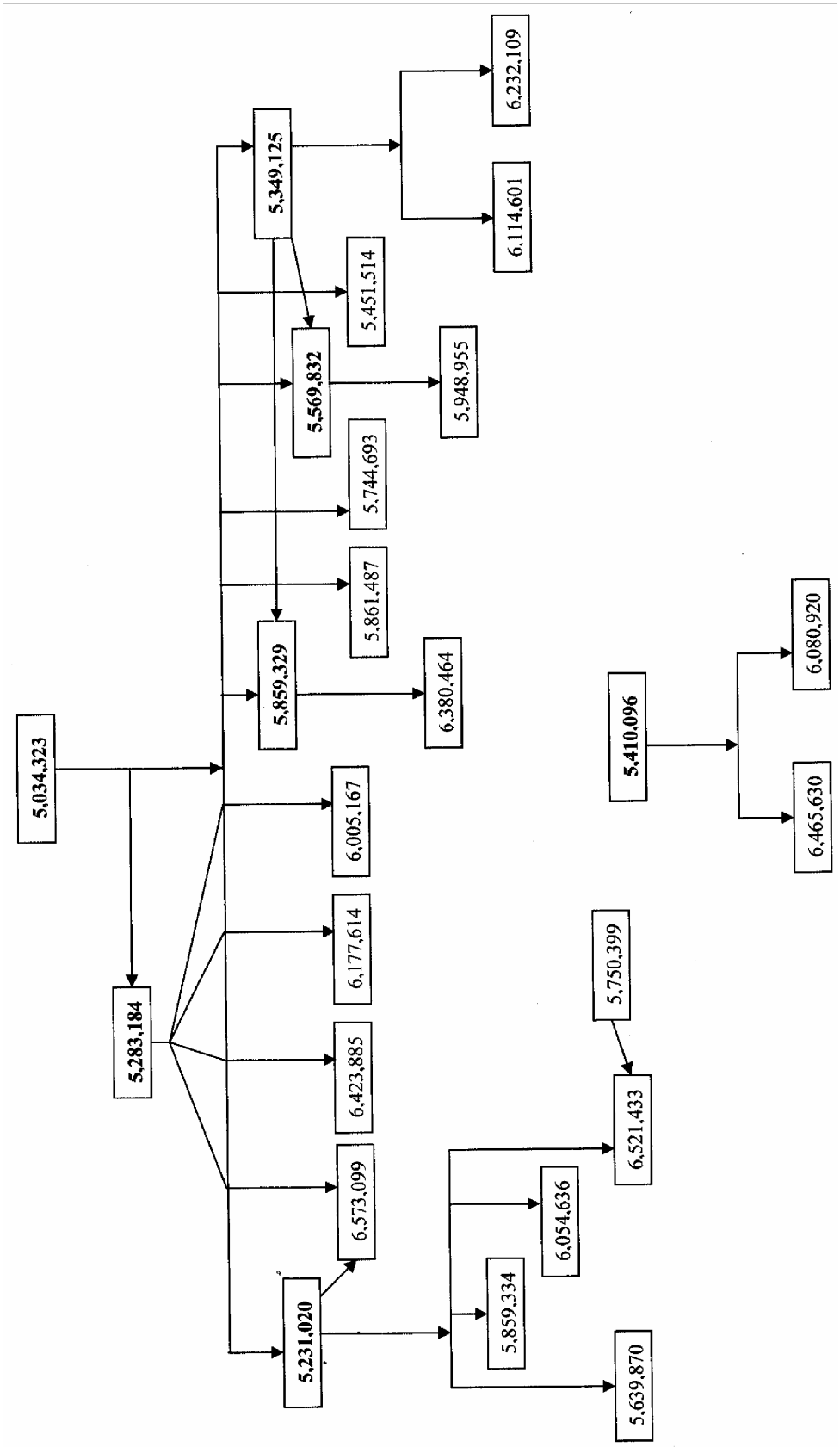
Conclusion

From the analysis of the patents on tea and the flavonoid pathway, it can be concluded: (i) there are no patents as such on the genetic engineering methods for increasing the synthesis of catechins and epicatechins, (ii) most of the patents are on various enzymes which are involved in the flavonoid pathway of plants for some other phenotype, (iii) the patents are very recent, most of them are granted after the year 2000. This implies that patent activity in this

Table 4—Major assignees with US and non US patents

Assignee	Country	Total no of patents	Groups which have patents
US patents			
DNA Plant Technology	US	3	B, G, M
Mogen International	Netherlands	1	B
Lipton, Division of Conopco Inc	US	1	C
International Flower Developments Pty Ltd	Australia	8	D, I, J, K, L, M
E I Du Pont de Nemours & Co	Germany	5	C, D, F, H
Suntory Flowers Ltd	Japan	2	E
Kyowa Hakko Kogyo Co Ltd	Japan	2	I
Korea Kumho Petrochemical Co Ltd	Korea	3	J
Centre National de la Recherche Scientifique	France	2	J
The Samuel Noble Foundation Inc and The Salk Institute for Biological Studies	US	2	C, K
Mitsui Chemicals Inc	Japan	1	N
Plant Bioscience Ltd	GB	1	N
Mars Incorporated	US	3	P
Indena SpA	Italy	1	P
Sapporo Breweries	Japan	1	B
CSIR	India	1	A
California Institute of Technology	US	1	G
Her Majesty, the Queen in Right of Canada as Rep. by the Minister of Agriculture and Agri Food	Canada	2	B, G
Genesis Research and development Corporation	New Zealand	2	I
Non US patents			
Sapporo Breweries	Japan	1	B
Vereniging Voor Christelijk (WE)	Netherlands	1	B
Iwate Prefecture Gov	Japan	2	B
Ishikawajima Harima Heavy Ind. Co Ltd	Japan	1	B
Hokko Chem. Ind. Co Ltd	Japan	1	C
Suntory Ltd	New Zealand	2	E
Samuel Roberts Noble Foundation	US	1	G
Plant Bioscience Ltd	United Kingdom	2	G, K
Forkman Gert and Martens Stefans	Germany	2	E
Agriculture Victoria Serv Pty And Agres Ltd	Australia	1	G
Tech Univ. Muenchen	Germany	1	E
Du Pont	Germany	1	H
General Hospital	US	1	B
Max Planck Gesellschaft	Germany	1	J
Korea Kumho Petrochem CoLtd	Korea	3	B, J
Unilever PLC and Unilever NV	GB and NL	1	M
BASF (AG)	Germany	1	M
Inst Medical W & E Hall	Australia	1	P
Mars Inc	US	1	P
Unilever Plc	GB	1	G

Patent Map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5,231,020
6,573,099
6,423,885
6,177,614
6,005,167
5,859,329
6,380,464
5,861,487
5,744,693
5,569,832
5,948,955
5,451,514
5,349,125
6,232,109
6,114,601
5,859,334
6,054,636
5,639,870
5,750,399
6,521,433
5,410,096
6,080,920
6,465,630

field is of recent origin and is increasing, (iv) International Flower Developments Pvt Ltd has the maximum number of patents, (v) US, Germany, Japan and Australia have the strongest patent activity, and (vi) the chalcone synthase group has the maximum number of patents.

The various enzymes and intermediates of the catechin biosynthetic pathway where there is no patent activity at all are: 4-Coumaryl CoA, Flavanone-3-hydroxylase, Flavonoid-3′-hydroxylase, 3′-Hydroxy dihydroflavonol, and Flavan-3-ols.

This identifies the research gaps in this area and brings out a scope for generating intellectual property if research is focused on the enzymes and intermediates mentioned (where there is no patent activity). The development of processes for these components will enable the interested research team to integrate all the steps resulting in the complete synthesis of catechins and epicatechins in tea plant.

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