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Global *Taxus* research trend and performance in science citation index from 1991 to 2010

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In this study, we aimed to evaluate the global scientific production of *Taxus* (yew) research, study the characteristics of *Taxus* research activities, and identify patterns, tendencies, and regularities of *Taxus*-related articles. Data were based on the online version of Science Citation Index Expanded (SCI-Expanded), from the Web of Science database. Articles referring to *Taxus* were assessed by the trend of publication output during 1991 to 2010. Globally, 2,916 papers were published during the 20-year study period. The most productive countries, institutions, Web of Science subject categories, and journals, as well as the most cited articles, were identified. The mainstream research on *Taxus* was in the plant sciences, biochemistry and molecular biology, cardiac and cardiovascular systems, biotechnology and applied microbiology. The G7 industrial countries, as well as China and India held the majority of total world production. Research on the various economically important *Taxus* species remained the hotspot during the 20-year study period, whereas that on the related topic "paclitaxel eluting stents" increased dramatically since 2002. With synthetic analysis of word in article title, author keyword, abstract, and key words Plus, it can be concluded that application of compounds derived from *Taxus* in clinical cardiology, pharmacology and oncology, and research related to *Taxus* chemistry, metabolism, cytology and microbiology is the ongoing *Taxus*-related research in the 21st century. Gaps are present in knowledge about the genomics, epigenomics, transcriptomics, proteomics, metabolomics and bioinformatics of *Taxus* and their endophytic fungi.

Key words: Science citation index (SCI), bibliometric, research trend, *Taxus.*

INTRODUCTION

Taxus (family: Taxaceae, common name: yew) is an economically important medicinal plant from which the anti-cancer paclitaxel and other useful taxanes are obtained. There is a long history of *Taxus* research. At the very beginning, only botanists were interested in studying this gymnosperm (Lefebvre, 1906); but gradually this research field became connected with multidisciplinary sciences (Preuss and Orth, 1965). *Taxus* has been studied by researchers in chemistry and biochemistry (Wani et al., 1971), plant biology and biotechnology (Yukimune et al., 1996), genetics and genomics (Trapp and Croteau, 2001), pharmacology and pharmacy (Ojima et al., 1999), microbiology (Stierle et al., 1993) and toxicology (Brown and Hull, 1951).

The first *Taxus* article in Science Citation Index Expanded (SCI-Expanded) was published in 1906

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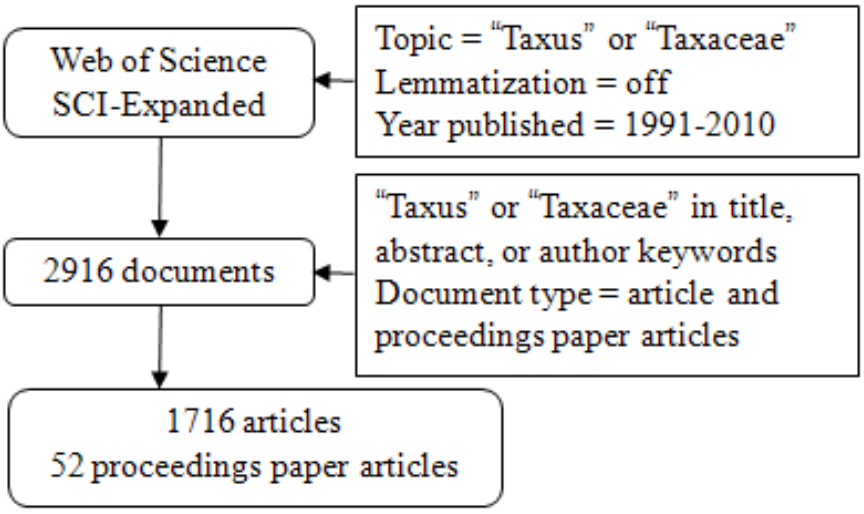

Figure 1. Schematic for searching *Taxus*-related research in Science Citation Index Expanded.

(Lefebvre), which is about "Taxicatine", a new glucoside from *Taxus baccata* (European yew). There are at least 10 species in the genus *Taxus* (Hao et al., 2008a, b), which are all endangered species but distinct in geographic distribution, biological characteristics and pharmaceutically useful components. The first *Taxus canadensis* (Canadian yew) article was published in 1917 (Dupler), which studied the gametophytes. The first *Taxus cuspidata* (Japanese yew; indigenous to China, Korea and Japan) article was about the response of cuttings to treatments containing powdered growth regulator and formate (Snyder, 1949). The first *Taxus brevifolia* (Pacific yew) article was not published until 1960 (Tyler), which was about the occurrence of taxine, the major alkaloid of the yew. The first *T.* × *media* (the hybrid of *T. baccata* and *T. cuspidata*) article was about the effects of chronic gamma irradiation on apical meristems (Miksche et al., 1961). All these early works were performed by the researchers of developed countries, thus the endemic species of the developing countries, such as *Taxus mairei*, *Taxus chinensis* and *Taxus yunnanensis* of China, *Taxus wallichiana* and *Taxus fuana* of China, India and Pakistan, *Taxus sumatrana* of Taiwan and Southeast Asia, and *Taxus globosa* of Mexico, had not been explored until 1980s (Miller et al., 1981). After these preliminary studies, the phytochemistry of yew trees became a hot topic. The first baccatin III (an intermediate taxane in the paclitaxel biosynthetic pathway) article was published in 1965 (Preuss and Orth). The taxane derivatives from the heartwood of *T. cuspidata* (Miyazaki et al., 1968) and *T. baccata* (Demarcan and Halsall, 1969) were for the first time reported respectively. The first milestone paper of *Taxus* anti-cancer research was published in 1971 (Wani et al.), which was about the isolation of the novel antitumor agent Taxol (commercial name of paclitaxel) from *T. brevifolia* and the structure of Taxol. Since then, the *Taxus* studies stride into a new era.

Some *Taxus* research hotspots, such as *Taxus* cell culture (Yukimune et al., 1996), paclitaxel-eluting stents (Grube et al., 2003), *Taxus* chemistry (Guenard et al., 1993), paclitaxel biosynthesis (Wildung and Croteau, 1996), semi-synthesis (Zamir et al., 1996), taxane-producing fungi (Stierle et al., 1993), taxoids analysis (Lavelle et al., 1993), and drug effects (Ketchum et al., 1999), have been noticed in recent years. *Taxus* cell culture systems, which are commercially successful, allow for sustainable production of *Taxus* secondary metabolites that were not limited by the low yields associated with natural harvest or the high cost associated with complex chemical synthesis (Wilson and Roberts, 2011). Semi-synthesis from the precursor baccatin III or 10-deacetylbaccatin III, which can be extracted from *Taxus* leaves, proved to be another appropriate method for commercial production of paclitaxel (Fu et al., 2009). Encouraging findings with endophytic fungi of *Taxus* resulted in much interest in the prospect of using endophytes as the producer of paclitaxel and other taxanes (Miller et al., 2008). However, there is no quantitative study addressing the global trend of *Taxus*-related research. In this study, we briefly review the history of *Taxus* studies and elucidate the current trend of related fields with bibliometric methods.

MATERIALS AND METHODS

Documents used in this study were derived from the SCI-Expanded Web of Science database of the Thomson Reuters. According to Journal Citation Reports (JCR), it indexes 8,005 journals with citation references across 174 scientific disciplines in 2010. Documents with "*Taxus*" and "Taxaceae" in titles, abstracts, authors' key words and KeyWords Plus were downloaded from 1991 to 2010 (Figure 1). Document information included names of authors,

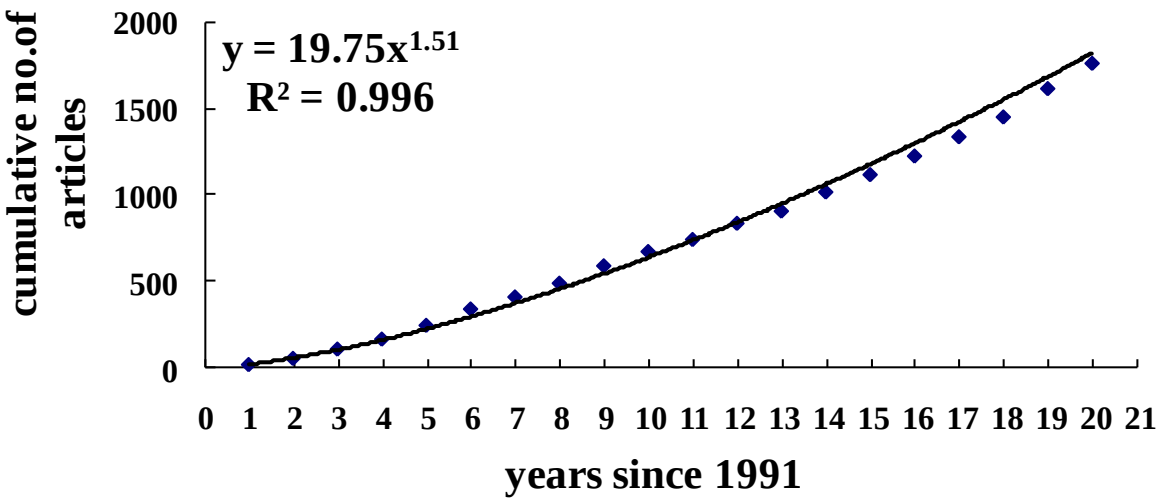

Figure 2. Cumulative numbers of articles by year during 1991-2010.

contact address, title, year of publication, author key words, abstract, KeyWords Plus, Web of Science subject categories, names of journals publishing the articles, and citations in each year for each article. The records were downloaded into Microsoft Excel 2007, and additional coding was manually performed for all data analysis.

Articles originating from England, Scotland, Northern Ireland, and Wales were reclassified as being from the United Kingdom (UK). Collaboration type was determined by the addresses of the authors, where the term "country independent article" was assigned if the researchers' addresses were from the same country. The term "internationally collaborative article" was designated to those articles that were coauthored by researchers from multiple countries (Chiu and Ho, 2005). The term "institute independent article" was assigned if the researchers' addresses were from the same institute. The term "inter-institutionally collaborative article" was assigned if authors were from different institutes (Li and Ho, 2008). The impact factor of a journal was determined for each document as reported in the JCR (2010).

RESULTS AND DISCUSSION

Document type and language of publication

The distribution of document types identified by Web of Science was analyzed. From this study, 11 document types were found in the total of 2,332 publications during the 20-year study period. Article (1,716) contained the most frequently used document type with 74% of all publications, which was followed by meeting abstracts (353; 15%) and reviews (94; 4.0%) and the remainder having less significance, including proceedings paper articles (52), notes (38), letters (35), editorial materials (27), news items (6), addition corrections (5), correction (5), and book chapter article (1). Only 1,768 original articles and proceedings paper articles were used for further analysis. Ninety-six percent (96%) of all these articles were published in English. Eleven (11) other languages were also used, including German (21), French (9), Russian (5), Japanese (5), Dutch (3), Spanish (3), Chinese (2), Portuguese (1), Cree (1), Croatian (1), and 12 unspecified. A significant correlation was found between the yearly cumulative number of articles (y) and the year from 1991 to 2010 (x), that is, $y = 19.8x^{1.51}$ ($r^2 = 0.996$; Figure 2).

Distribution of output in subject categories and journals

Based on the classification of subject categories in Web of Science, the publication output data of *Taxus* research was distributed in 91 subject categories in JCR science edition during the last 20 years. The 10 top productive subject categories are shown in Table 1. Moreover, the annual publications of the top four productive subject categories are analyzed in Figure 3. The number of scientific articles per category exhibited remarkable fluctuation during the time period covered. Plant science was held primacy until 2004, and was exceeded by cardiac and cardiovascular systems from 2005, due to an increased upsurge of the studies of the paclitaxel-eluting stents. Biochemistry and molecular biology followed plant sciences until 1999 and was caught up by biotechnology and applied microbiology from 2001. Publication of cardiac and cardiovascular systems increased rapidly since the first article in 2002. Plant science and biochemistry and molecular biology represent the basic aspects of *Taxus*-related research, while cardiac and cardiovascular systems and biotechnology and applied microbiology represented the applied fields of *Taxus*-related research. It is expected that the total number of articles in the former would be overtaken by that of the latter in the next 20 years.

Table 1. Top ten Web of Science categories.

Web of Science category	TP	%
Plant Sciences	430	25
Biochemistry and Molecular Biology	297	17
Cardiac and Cardiovascular Systems	212	12
Biotechnology and Applied Microbiology	204	12
Medicinal Chemistry	192	11
Pharmacology and Pharmacy	190	11
Ecology	110	6.3
Organic Chemistry	109	6.2
Multidisciplinary Chemistry	101	5.8
Analytical Chemistry	75	4.3

TP, Total articles.

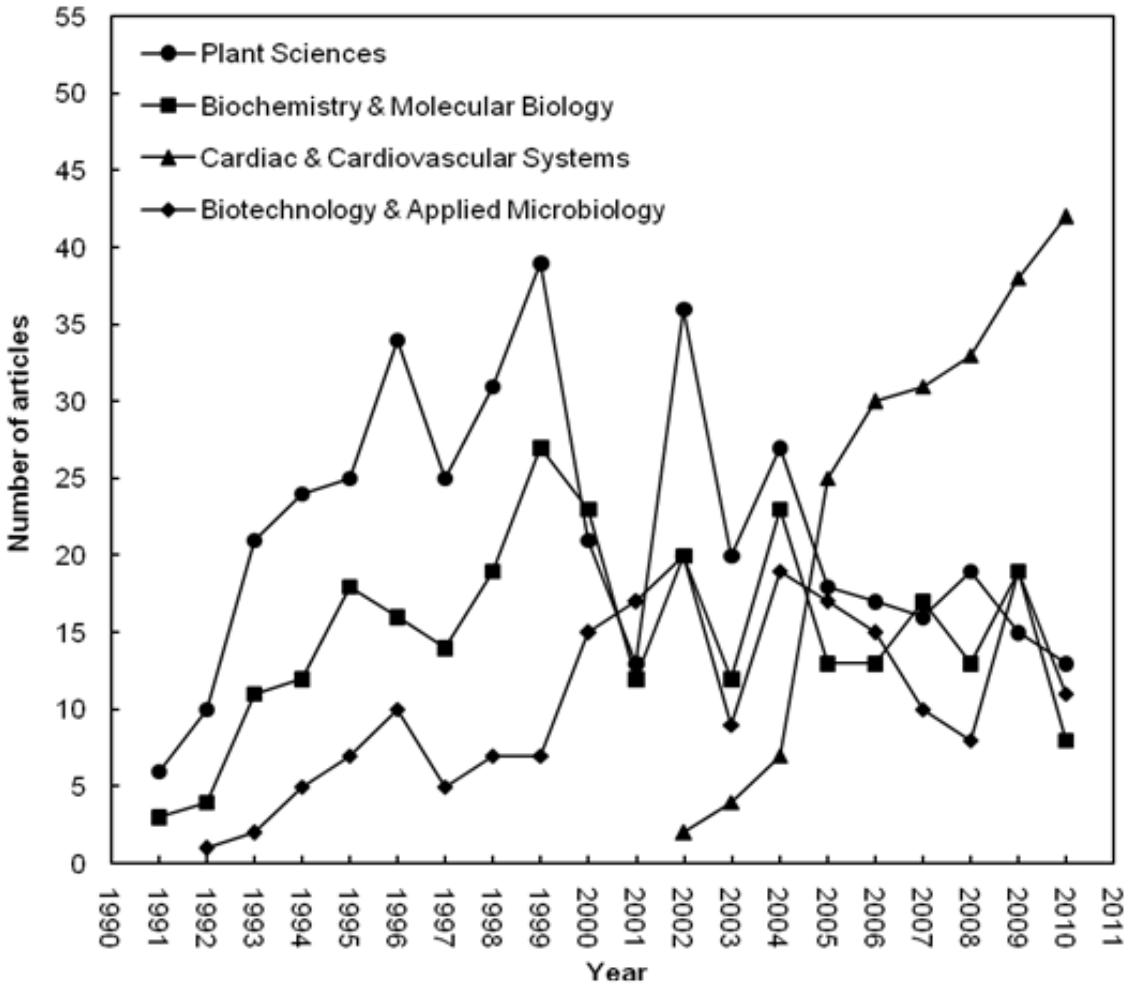

Figure 3. Growth trends of top four subject categories containing more than 200 articles.

In total of 1,768 articles were published in 562 journals. The top 11 productive journals through the recent 20 years are presented in Table 2. As the leading journal of this particular research field, *Phytochemistry* published the most articles with 85 publications comprising 4.8% of all the articles, followed by *Journal of Natural Products*

Table 2. Top 11 Journals.

Journal	IF2010	TP (%)	Web of Science categories
Phytochemistry	3.15	85 (4.8)	Biochemistry and Molecular Biology; Plant Sciences
Journal of Natural Products	2.872	68 (3.8)	Plant Sciences; Medicinal Chemistry; Pharmacology and Pharmacy
Biotechnology Letters	1.768	33 (1.9)	Biotechnology and Applied Microbiology
American Journal of Cardiology	3.68	30 (1.7)	Cardiac and Cardiovascular Systems
Journal of the American College of Cardiology	14.292	28 (1.6)	Cardiac and Cardiovascular Systems
JACC-Cardiovascular Interventions	5.862	27 (1.5)	Cardiac and Cardiovascular Systems
Planta Medica	2.369	25 (1.4)	Plant Sciences; Medicinal Chemistry; Pharmacology and Pharmacy
Tetrahedron	3.011	23 (1.3)	Organic Chemistry
Catheterization and Cardiovascular Interventions	2.398	21 (1.2)	Cardiac and Cardiovascular Systems
Biotechnology and Bioengineering	3.7	20 (1.1)	Biotechnology and Applied Microbiology
Circulation	14.429	20 (1.1)	Cardiac and Cardiovascular Systems; Hematology; Peripheral Vascular Disease

IF2010: Impact factor in 2010.

and *Biotechnology Letters*, contributing 3.8 and 1.9% of all the journal articles, respectively.

Distribution of institutes and countries

During the study period, the Boston Scientific Corporation of the USA had the best outputs, which published the most articles (76) and completed the most cooperative articles (Table 3). On the other hand, the first authored and corresponding authored articles of the Tianjin University of China were the most, which also completed the most independent articles. The major contributor is the research group led by YJ Yuan (Xiao et al., 2009; Han and Yuan, 2009), who studied the large scale taxane production via *Taxus* cell culture. Tohoku University (61) of Japan and Chinese Academy of Sciences (51) were the most productive university and institute respectively. Tohoku University ranked second in the independent articles, followed by Washington State University of the USA. The group led by R Croteau of Washington State University is the major contributor in decoding the paclitaxel biosynthesis (Hampel et al., 2009; Long et al., 2008), from which the paradigm of isoprenoid biosynthesis is established: a linear polyisoprenoid precursor is cyclized to a hydrophobic scaffold, which is then modified by the addition of oxygen-based functional groups. QW Shi was the major contributor of both Tohoku University, University of Quebec of Canada, and Hebei Medical University of China (Ni et al., 2011; Shi et al., 2005; Shi et al., 2000), who studied the chemical ingredients of *T. cuspidata*. Columbia University of the USA ranked second in the cooperative publications, followed by the Cardiovascular Research Foundation of the USA. These two institutions and the Boston Scientific Corporation focus on the research and development of the paclitaxel-eluting stents.

The contribution of different countries/territories was estimated by the location of the affiliation of at least one author of the published papers. The top 20 countries/territories ranked by number of publications are listed in Table 4. Two North American countries, 10 European countries, seven Asian countries/territories, and Australia ranked in the top 20 of articles. There was still no African and South American country getting into the top productive countries. There are some leading institutions steering the *Taxus*-related research in China and India (Table 3). Taking the Chinese Academy of Sciences, for example; it is a recognized leading center of expertise in the fields of medicinal plants, pharmaceutical biotechnology and multidisciplinary chemistry whose research results of the endemic *Taxus* species were used to underpin policy on biotechnology, public health and biodiversity. G7 (Except UK and France), China and India had high productivity in independent articles, first authored, and corresponding authored articles, owning the percentage of 73, 70 and 69%, respectively. Domination of developed countries in publication was not surprising since this pattern has occurred in most scientific fields (Li et al., 2011; Chuang et al., 2011). The rise of China and India in many research fields are also well known (Fu et al., 2011; Chuang et al., 2011). The number of research papers reflects the increasing activity and academic level of these developing countries. The USA exhibited its predominance in global *Taxus* research and showed the greatest counts of world publications, comprising 30% of the total articles. It also had the most-frequent partners, accounting for 42% of all the international collaborative articles. Although, the internationally collaborative articles took only 28% of its total country articles, which was far away from Japan (41%), Germany (50%), and Italy (48%). The increasing speed of articles of the USA remained unstable all through (Figure 4), with the highest peak from 2009 to 2010 and the second highest peak in 1996. China followed closely behind the USA, and ranked second in terms of all the measurements mentioned above. With the increasing research funds, both basic

Table 3. Top 23 most productive institutions based on the number of articles published.

Institution	TP	TPR (%)	SPR (%)	CPR (%)	FPR (%)	RPR (%)	C%
Boston Scientific Corporation, USA	76	1 (4.3)	69 (0.26)	1 (7.5)	53 (0.34)	49 (0.32)	97
Tohoku University, Japan	61	2 (3.5)	2 (3.4)	7 (3.5)	3 (2.3)	6 (1.6)	57
Tianjin University, China	56	3 (3.2)	1 (6.4)	64 (0.71)	1 (3.2)	1 (3.3)	13
Chinese Academy of Sciences, China	51	4 (2.9)	5 (1.8)	5 (3.7)	4 (2.2)	2 (2.2)	73
Columbia University, USA	49	5 (2.8)	49 (0.39)	2 (4.6)	16 (0.85)	14 (0.95)	94
Washington State University, USA	47	6 (2.7)	3 (3.0)	11 (2.4)	2 (2.3)	3 (1.9)	51
Chinese Academy of Medical Sciences, China	46	7 (2.6)	32 (0.52)	4 (4.2)	5 (1.8)	8 (1.6)	91
Cardiovascular Research Foundation, USA	43	8 (2.4)	N/A	3 (4.3)	12 (0.91)	17 (0.88)	100
Hebei Medical University, China	37	9 (2.1)	113 (0.13)	6 (3.6)	7 (1.5)	6 (1.6)	97
University of Quebec, Canada	34	10 (1.9)	49 (0.39)	8 (3.1)	7 (1.5)	3 (1.9)	91
Huazhong University of Science and Technology, China	33	11 (1.9)	4 (2.7)	30 (1.2)	6 (1.5)	5 (1.7)	36
Queens University, Canada	28	12 (1.6)	N/A	9 (2.8)	248 (0.057)	225 (0.063)	100
McGill University, Canada	26	13 (1.5)	N/A	10 (2.6)	62 (0.28)	225 (0.063)	100
Central Institute of Medicinal and Aromatic Plants, India	25	14 (1.4)	10 (1.0)	16 (1.7)	10 (1.0)	10 (1.1)	68
National Sun Yat Sen University, Taiwan	25	14 (1.4)	8 (1.4)	23 (1.4)	9 (1.1)	9 (1.2)	56
Hokkaido University, Japan	24	16 (1.4)	7 (1.6)	30 (1.2)	12 (0.91)	11 (1.0)	50
Academia Sinica, China	21	17 (1.2)	49 (0.39)	14 (1.8)	21 (0.63)	49 (0.32)	86
Cornell University, USA	21	17 (1.2)	15 (0.91)	23 (1.4)	10 (1.0)	27 (0.57)	67
Peking Union Medical College, China	21	17 (1.2)	N/A	12 (2.1)	248 (0.057)	225 (0.063)	100
Fudan University, China	21	17 (1.2)	32 (0.52)	16 (1.7)	19 (0.68)	19 (0.76)	81
Cleveland Clinical Foundation, USA	21	17 (1.2)	113 (0.13)	13 (2.0)	148 (0.11)	121 (0.13)	95
USDA ARS, USA	20	22 (1.1)	19 (0.78)	23 (1.4)	34 (0.51)	19 (0.76)	70
Erasmus Medical Center, Netherlands	20	22 (1.1)	32 (0.52)	20 (1.6)	16 (0.85)	14 (0.95)	80

TP, The number of total articles; TPR (%), the rank and share in total articles; SPR (%), CPR (%), FPR (%), RPR (%), the rank and percentage of single institute articles, inter-institutionally collaborative articles; first author articles; corresponding author articles in total articles; %C, institute collaboration percentage, the percentage of inter-institutionally collaborative articles in total articles for each institute; N/A, not applicable.

and clinical aspects of the *Taxus*-related research are emphasized and strengthened in China.

Research trend and hotspots

Distribution of words in article title and abstract

Word statistical analysis was used to find the research tendency of this field. The statistical analysis of word in title, abstract, author key words, and the KeyWords Plus might facilitate discovering directions of science (Li et al., 2011; Suk et al., 2011; Wang et al., 2011). The results of the statistical analysis help us find the possible research trend and hotspots. The title of an article always includes the information that an author would most like to express to the readers, because it would be browsed by all the readers at first. It could be used to make inferences of the scientific literature or to identify the subjective focus and emphasis specified by authors. In this study, we statistically analyzed all the single words in the title of *Taxus*-related articles. All empty words including “of”, “in”, “and”, “the”, “a”, “for”, “with”, “by” and “to” are discarded in the paper title and abstract analysis. The 20 most frequently used single words in title are displayed in Table 5. The usually used title words, except for the searching words, can be divided into three groups according to their appearing features. The first group consisted of “taxol”, “cultures” and “baccata”, which ranked as the top three in the total appearance time and implied that the drug Taxol and its analogs (Gueritte-Voegelein et al., 1991), callus and cell cultures of various *Taxus* tissues (Yukimune et al., 1996), together with the most commonly exploited species *T. baccata* (Hulme, 1996), were the emphasis of the *Taxus*-related research. The second group was made up of “taxane”, “production”, “cuspidata” and “chinensis”,

Table 4. Top 20 countries based on the number of articles published.

Country	TP	TPR (%)	SPR (%)	CPR (%)	FPR (%)	RPR (%)	C%
USA	530	1 (30)	1 (27)	1 (42)	1 (25)	1 (24)	28
China	369	2 (21)	2 (19)	2 (31)	2 (19)	2 (19)	29
Japan	181	3 (10)	3 (7.6)	3 (21)	3 (8)	3 (7.1)	41
Germany	139	4 (7.9)	5 (4.9)	4 (20)	5 (4.8)	5 (5.4)	50
Canada	134	5 (7.6)	4 (6.1)	6 (14)	4 (5.6)	4 (5.6)	36
Italy	96	6 (5.5)	7 (3.5)	7 (13)	7 (3.9)	7 (3.7)	48
India	77	7 (4.4)	6 (4.7)	17 (2.9)	6 (4.0)	6 (4.3)	13
UK	71	8 (4.0)	16 (1.1)	5 (16)	15 (1.8)	15 (1.6)	77
France	69	9 (3.9)	11 (2.3)	8 (10)	10 (2.5)	13 (2.3)	52
Netherlands	58	10 (3.3)	13 (2.0)	9 (8.7)	9 (2.6)	11 (2.4)	52
Korea	58	10 (3.3)	8 (3.3)	14 (3.5)	8 (3.1)	8 (3.2)	21
Poland	56	12 (3.2)	10 (2.5)	11 (6.1)	12 (2.4)	9 (2.6)	38
Spain	48	13 (2.7)	12 (2.0)	12 (5.5)	11 (2.4)	11 (2.4)	40
Taiwan	45	14 (2.6)	9 (2.6)	20 (2.3)	13 (2.3)	10 (2.5)	18
Turkey	35	15 (2.0)	13 (2.0)	22 (2.0)	14 (1.9)	14 (2.0)	20
Belgium	31	16 (1.8)	20 (0.57)	10 (6.7)	19 (0.68)	21 (0.51)	74
Switzerland	23	17 (1.3)	17 (0.78)	14 (3.5)	17 (0.91)	17 (0.95)	52
Iran	21	18 (1.2)	15 (1.2)	28 (1.2)	16 (1.1)	16 (1.2)	19
Australia	19	19 (1.1)	23 (0.35)	13 (4.1)	22 (0.45)	20 (0.63)	74
Pakistan	16	20 (0.91)	17 (0.78)	24 (1.4)	20 (0.63)	19 (0.69)	31

TP, The number of total articles; % TP, the share in total articles; SPR (%), CPR (%), FPR (%), RPR (%), the rank and percentage of single country articles, internationally collaborative articles, first author articles, corresponding author articles in total articles; %C, country collaboration percentage, the percentage of collaborative articles in total articles for each country.

whose frequency closely followed the first group. Indeed other taxanes, besides paclitaxel and including the analogs and derivatives of paclitaxel, were intensely studied (Bissery et al., 1991). *T. cuspidata* and *T. chinensis*, the endemic species of China, are frequently used in the basic studies of *Taxus* chemistry (Eisenreich et al., 1996), metabolism (Ketchum et al., 1999), physiology, enzymology (Kaspera and Croteau, 2006), and microbiology (Kumaran et al., 2010), and in the cell culture production of taxanes (Lee et al., 2010). Words “stent(s)”, “coronary”, and “paclitaxel-eluting” from the third group had a prominent character: their percentage of appearance time in the recent five years increases significantly, which indicated that the paclitaxel-eluting stents were frequently used recently in the treatment of coronary artery diseases (Joner et al., 2006). These words probably represent one of the frontlines of the *Taxus*-related field.

Zhang et al. (2010) and Li et al. (2011) first used the analysis of single words in abstracts to make specific inferences about the scientific literature and identify the subjective focus and emphasis specified by authors. As with the distribution of paper titles, “taxol”, “cell(s)”, and “baccata” were among the most frequently used single words during 1991 to 2010. Moreover, “isolated”, “analysis”, and “species” were also emphasized in abstracts. Isolation, purification and phytochemical analyses of paclitaxel and taxoids from the respective *Taxus* species and endophytic fungi are the hot issues (Guenard et al., 1993; Baloglu and Kingston, 1999).

Distribution of author’s key words

The author key words analysis could offer the information of research trend that is concerned by researchers (Zhang et al., 2010). The statistical analysis of author key words might help discover directions of scientific research, and prove important for monitoring development of science and programs. Author keywords appeared in the articles referring to *Taxus* were calculated and ranked by total 20-year and four five-year

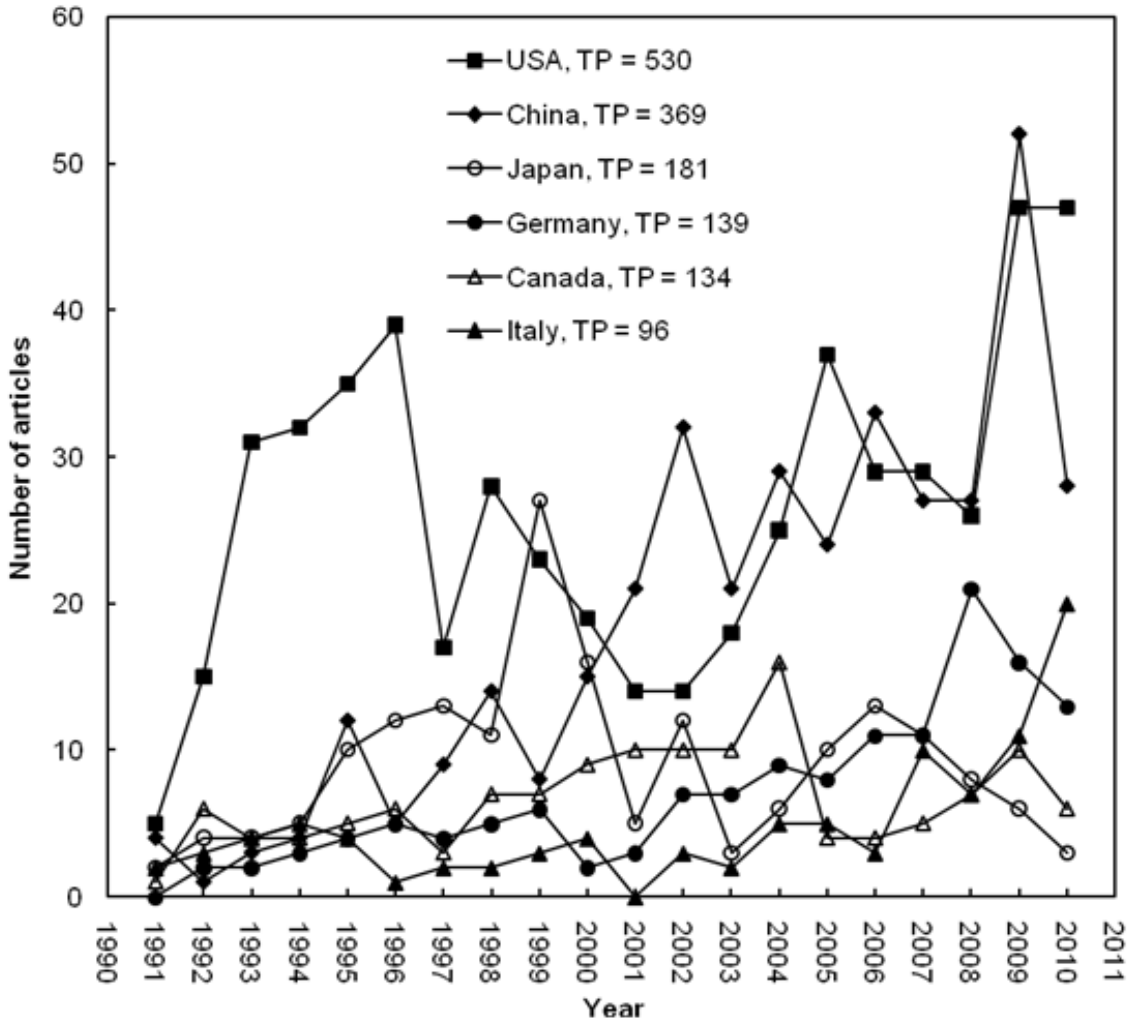

Figure 4. Publication growth of the top six countries.

sub-periods. The author keywords that appeared more than 23 times in all in the last 20 years are displayed in Table 6. Synthetically analyzing these words, we found that *Taxus* had infiltrated into many subject categories (e.g., biotechnology, cardiology, and phytochemistry). Taking the most often used 20 author key words, for example, “plant cell culture” was mainly from biotechnology; “restenosis” and “drug-eluting stent(s)” came from cardiology; “taxane(s)” and “taxoid(s)” might come from phytochemistry and analytical chemistry. Different *Taxus* species have distinct metabolic profiles (Ge et al., 2008) and thus should be exploited with different strategies. Among various *Taxus* species, *T. cuspidata* was most commonly studied (Ketchum et al., 1999; Ge et al., 2008), followed by *T. baccata* (Parmar et al., 1999), *T. chinensis* (Eisenreich et al., 1996), *T. mairei* (endemic in China; Hao et al., 2011a, b), *T. yunnanensis* (endemic in China; Parmar et al., 1999), *T. canadensis* (Ketchum et al., 1999), while *T. wallichiana* (Himalayan yew; Parmar et al., 1999), *T. brevifolia* (Trapp and Croteau, 2001) and *T.* × *media* (Parmar et al., 1999; Hao et al., 2008) were less commonly studied. *T. floridana* and *T. globosa* were rarely studied. Different *Taxus* tissues have distinct gene expression patterns and taxane contents (Hao et al., 2011b). Among various *Taxus* tissues, the stem bark was most frequently studied (Wani et al., 1971; Eldridge et al., 2002), followed by needles (Ge et al., 2008; Hao et al., 2011a), pollen (Zimmermann, 2010), seeds (Huo et al., 2007), and roots (Onrubia et al., 2011; Hao et al., 2011b).

Different from segmenting the title into single words in paper title analysis, in this section, we preserved the intact words that the authors want to transmit to the readers. Systemically analyzing the top 200 most frequently appearing author keywords, we could roughly draw the research trend of each sub-period. During the first sub-period (1991 to 1995) the research hotspot mainly focused on two branches. One was taxanes, taxoids, and diterpenoids, especially on anti-cancer-related research (Huizing et al., 1995). In 1993, “phase-II

Table 5. Top 20 most frequently used words in article title during 1991-2010 divided into four five-year periods.

Words in title	TP	91-10 R (%)	91-95 R (%)	96-00 R (%)	01-05 R (%)	06-10 R (%)
Taxus	910	1 (51)	3 (16)	1 (64)	1 (60)	1 (50)
Taxol	224	2 (13)	1 (28)	4 (14)	5 (13)	16 (5.4)
Yew	185	3 (10)	4 (13)	2 (18)	9 (8.3)	12 (6.3)
Cultures	154	4 (8.7)	34 (2.0)	9 (8.4)	2 (18)	25 (4.8)
Baccata	151	5 (8.5)	111 (0.82)	5 (11)	8 (9.4)	7 (9.1)
Stent	139	6 (7.9)	N/A	N/A	16 (5.1)	2 (18)
Taxane	138	7 (7.8)	6 (10)	3 (15)	13 (6)	36 (3.4)
Production	138	7 (7.8)	12 (5.3)	9 (8.4)	6 (13)	22 (4.9)
Cuspidata	126	9 (7.1)	N/A	6 (11)	11 (7.2)	10 (7.3)
Chinensis	123	10 (7.0)	N/A	15 (6.5)	4 (15)	26 (4.3)
Suspension	121	11 (6.8)	N/A	18 (4.7)	3 (17)	32 (3.9)
Paclitaxel	118	12 (6.7)	15 (3.7)	11 (7.7)	10 (7.8)	12 (6.3)
Cell	116	13 (6.6)	111 (0.82)	12 (7.5)	7 (11)	22 (4.9)
Stents	116	13 (6.6)	N/A	N/A	21 (4.5)	3 (15)
Coronary	111	15 (6.3)	N/A	N/A	24 (3.6)	4 (15)
Taxanes	105	16 (5.9)	2 (18)	13 (7.0)	29 (3.1)	50 (2.6)
Taxoids	99	17 (5.6)	8 (5.7)	8 (8.6)	13 (6.0)	38 (3.2)
Paclitaxel-eluting	99	17 (5.6)	N/A	N/A	18 (4.9)	5 (12)
Needles	92	19 (5.2)	8 (5.7)	13 (7.0)	25 (3.4)	19 (5.1)
Analysis	90	20 (5.1)	15 (3.7)	42 (2.6)	18 (4.9)	9 (7.4)

TP, The number of total article; R (%), the rank and percentage of words in article title in total articles; N/A, not applicable.

study of taxol in patients with untreated advanced non-small-cell lung-cancer" was published in *Journal of the National Cancer Institute* (Murphy et al., 1993); in 1994, "total synthesis of taxol" was published in *Nature* (Nicolaou et al., 1994). The two papers were cited 497 and 613 times, respectively, since they were published to 2010. Other frequently used author keywords, such as "HPLC" and "tissue culture" indicated that the other research branch was research techniques. HPLC was commonly used in the isolation, purification and analysis of various taxanes (Cardellina, 1991); callus culture was more prevalent than suspension cell culture. The most commonly studied species were *T. cuspidata*, *T. baccata* and *T. brevifolia* (Appendino, 1995; Wildung and Croteau, 1996). Compared with the first sub-period, in the next five years (1996-2000), *T. mairei* became the second most frequently used species, which, as well as *T. chinensis*, *T. yunnanensis* and *T. canadensis*, were more frequently used in the semisynthesis and cell culture production of paclitaxel (Eisenreich et al., 1996; Srinivasan et al., 1996). The elicitor, methyl jasmonate, was used to induce the paclitaxel biosynthesis in the cell culture during these five years (Yukimune et al., 1996; Ketchum et al., 1999). In the third sub-period (2001-2005), the key research trend changed. *T. chinensis* became the most frequently used species (Lan et al., 2003). Although research involved in "plant cell culture" and "elicitation" still dominated this field, the apoptosis in *Taxus* cells was studied in depth (Kim et al., 2005). Research emphasis never stopped changing. For example, "taxol biosynthesis" was paid more attention to in this sub-period, meanwhile, paclitaxel- eluting stents were implanted to prevent and treat restenosis of coronary artery (Joner et al., 2006). In the period of 2006 to 2010, *T. baccata* became the most frequently used species (Jaramillo-Correa et al., 2010), followed by *T. cuspidata* and *T. yunnanensis* (Hao et al., 2009). More papers about drug-eluting stents were published (Finn et al., 2007). During the whole study period, rankings of some author key words shifted dramatically. For instance, "endophytic fungi", which could not be found as the author keyword between 1991 and 1995, soared to "151st" in 1996-2000, and "22nd" in 2006-2010. The *Taxus* endophytic fungi have been an alternative source of useful taxanes and drug intermediates (Kumaran et al., 2010), and their isolation, culture and secondary metabolism were paid more attention to. In early times of the study period, Stierle et al. (1993) isolated *Taxomyces andreanae* from the phloem (inner bark) of the Pacific yew, *T. brevifolia*, which produced paclitaxel and related compounds when grown in a semi-synthetic liquid medium. *Pestalotiopsis microspora* was isolated from the inner bark of a small limb of Himalayan yew, *T. wallachiana*, and was shown to produce paclitaxel in mycelial culture (Strobel et al., 1996). Then the fungi-related articles went into a booming period. On the contrary, some author key words were losing their research potency in the study period since they gradually

Table 6. Top 20 most frequently used author keywords during 1991-2010 divided into four five-year periods.

Author's key words	TP	91-10 R (%)	91-95 R (%)	96-0 R (%)	1-5 R (%)	6-10 R (%)
Taxaceae	173	1 (14)	2 (25)	1 (26)	4 (9.5)	3 (7.4)
Paclitaxel	168	2 (14)	12 (3.8)	3 (14)	1 (18)	1 (13)
Taxol	166	3 (13)	1 (33)	2 (16)	2 (12)	2 (7.8)
Taxus cuspidata	93	4 (7.5)	7 (6.2)	4 (10)	5 (8.3)	9 (6.0)
Taxus	92	5 (7.4)	4 (12)	8 (7.6)	6 (7.1)	6 (6.4)
Taxus baccata	76	6 (6.1)	12 (3.8)	8 (7.6)	8 (5.6)	8 (6.2)
Taxanes	74	7 (6.0)	3 (13)	5 (9.1)	9 (5.0)	16 (3.0)
Yew	72	8 (5.8)	5 (11)	10 (5.8)	9 (5.0)	11 (5.0)
Taxus chinensis	60	9 (4.8)	65 (0.77)	11 (5.1)	3 (10)	20 (2.2)
Taxoids	53	10 (4.3)	6 (6.9)	6 (8.3)	15 (3.3)	22 (2.0)
Restenosis	51	11 (4.1)	N/A	N/A	12 (4.2)	3 (7.4)
Stents	46	12 (3.7)	N/A	N/A	12 (4.2)	6 (6.4)
Taxane	43	13 (3.5)	12 (3.8)	11 (5.1)	20 (2.4)	15 (3.2)
Drug-eluting stent	38	14 (3.1)	N/A	N/A	50 (0.89)	5 (7.0)
Plant cell culture	37	15 (3)	65 (0.77)	25 (1.8)	7 (6.5)	26 (1.8)
Taxus mairei	36	16 (2.9)	N/A	7 (8.0)	20 (2.4)	38 (1.2)
Taxus yunnanensis	35	17 (2.8)	32 (1.5)	17 (3.3)	14 (3.6)	19 (2.4)
Drug-eluting stents	29	18 (2.3)	N/A	N/A	76 (0.59)	10 (5.4)
Taxoid	25	19 (2.0)	27 (2.3)	13 (4.3)	25 (1.5)	43 (1.0)
Taxus canadensis	24	20 (1.9)	65 (0.77)	14 (3.6)	33 (1.2)	26 (1.8)

TP, The number of total article; R (%), the rank and percentage of author key words in total articles; N/A, not applicable.

disappeared in the list of frequently used author keywords. Taking "bark" for example, it ranked 19th in 1991 to 1995; fell to 50th in 2001 to 2005; and then straightly descended to 254th in 2006 to 2010, implying that the stem bark is not the drug source any more. This kind of author key word included "taxus brevifolia", "baccatin III", "needles", and "cephalomannine".

Distribution of key words plus

The KeyWords Plus in the SCI database supplied additional search terms extracted from the titles of articles cited by authors in their bibliographies and footnotes (Garfield, 1990a, b). The KeyWords Plus analysis as an independent supplement reveals the article contents with more details. The distribution of the KeyWords Plus with its rank and percentage in different periods is available upon request. As a whole, the research tread revealed by KeyWords Plus was consistent with author keywords. "taxol", "brevifolia", and "taxanes" were also emphases of KeyWords Plus in the study period. However, KeyWords Plus gave special prominence to "growth", "needles", "methyl jasmonate", and "biosynthesis." Meanwhile, it weakened the leading status of "taxus", "taxaceae", and "yew", which was different from author keywords. KeyWords Plus are usually more concerned about the novel research direction than the mature direction in the field (Garfield, 1990a, b). For example, "implantation" method could combine with the eluting paclitaxel and replace the traditional stents, which was a rapidly developing direction in the treatment of the coronary artery disease (Colombo et al., 2003; Grube et al., 2003). Lots of cell culture research had studied the "growth" of the taxane-producing cells (Fett-Neto et al., 1994). Other words, such as "methyl jasmonate", "suspension-cultures", and "biosynthesis", were all closely correlative to the cell culture production of paclitaxel and other taxoids (Yukimune et al., 1996; Ketchum et al., 1999), which, along with the semisynthesis, is providing the practical process for the large-scale drug production (Lee et al., 2010).

Conclusion and perspective

It is no doubt that the *Taxus* research is an exciting and revolutionary multidisciplinary field at the center of many current key scientific issues. In this study, we obtained some significant points on the worldwide research trends throughout the period from 1991 through 2010. The effort provided a panorama, as well as clues to the impacts of the *Taxus*-related topic. English was by far the dominant language, while 11 other languages were also used. The *Taxus*-related research and development became more globally connected. The Boston Scientific Corporation was the pioneer in the field of the paclitaxel-eluting

stents, while Tohoku University of Japan and Tianjin University of China were leading in phytochemistry and cell culture studies respectively. The G7, together with China and India, are strong in this field. They had not only the absolute ascendancy of publication, but also the most-frequent research partners. Overall 1768 articles were published in 562 journals in 91 subject categories with a great diversity. The mainstream of *Taxus*-related research was in plant science. Systematically analyzing the distribution of paper title, abstract, author key word, and Key Words Plus, we suggest that *Taxus*-related research mainly focused on two branches. One was phytochemistry and biotechnology, especially on paclitaxel biosynthesis, semi-synthesis and cell culture production of taxanes, and the other was paclitaxel-eluting stents. Although semi-synthesis and subsequent plant cell culture-based production efforts have decreased the need for harvesting the endangered yew tree, production still depends on plant-based processes. Recent developments in metabolic engineering and synthetic biology offer new pathways for the overproduction of complex natural products by optimizing more technically amenable microbial hosts (e.g., *E. coli*; Ajikumar et al., 2010, Morrone et al., 2010). Moreover, the crystal structure of the taxadiene synthase, the enzyme that catalyzes the first committed step of paclitaxel biosynthesis, and the evolution of modular architecture in terpene biosynthesis, have been elucidated (Köksal et al., 2011), which will accelerate the study of *Taxus* metabolism and physiology, and promote the research and development of the microbial cell factory. The bibliometric method can help relevant researchers realize the scenario of global *Taxus*-related research, and establish the further research direction. Based on the bibliometric results, we find that gaps are present in knowledge about the genomics, epigenomics, transcriptomics, proteomics, metabolomics and bioinformatics of *Taxus* and their endophytic fungi. Systems biology and various omics technologies will play an increasingly important role in the coming decades. This study provides a paradigm of assessing research performance and trend of any medicinal plants with bibliometric methods.

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