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Anti-Cancer Agents in Medicinal Chemistry, 2019, *19*, 194-203

RESEARCH ARTICLE

What Makes Species Productive of Anti-Cancer Drugs? Clues from Drugs' Species Origin, Druglikeness, Target and Pathway

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Abstract: ***Background*:** Despite the substantial contribution of natural products to the FDA drug approval list, the discovery of anti-cancer drugs from the huge amount of species on the planet remains looking for a needle in a hay-stack.

***Objective*:** Drug-productive clusters in the phylogenetic tree are thus proposed to narrow the searching scope by focusing on much smaller amount of species within each cluster, which enable prioritized and rational bioprospecting for novel drug-like scaffolds. However, the way anti-cancer nature-derived drugs distribute in phylogenetic tree has not been reported, and it is oversimplified to just focus anti-cancer drug discovery on the drug-productive clusters, since the number of species in each cluster remains too large to be managed.

***Methods*:** In this study, 260 anti-cancer drugs approved in the past 70 years were comprehensively analyzed by hier-archical clustering of phylogenetic distribution.

***Results*:** 207 out of these 260 drugs were derived from or inspired by the natural products isolated from 58 species. Phylogenetic distribution of those drugs further revealed that nature-derived anti-cancer drugs originated mostly from drug-productive families that tend to be clustered rather than scattered on the phylogenetic tree. Moreover, based on their productivity, drug-producing species were categorized into productive (CPS), newly emerging (CNS) and less-productive (CLS). Statistical significances in druglikeness between drugs from CPS and CLS were observed, and drugs from CNS were found to share similar drug-like properties to those from CPS.

***Conclusion*:** This finding indicated a great raise in drug approval standard, which suggested us to focus bioprospect-ing on the species yielding multiple drugs and keeping productive for long period of time..

ARTICLE HISTORY

Received: July 11, 2017
Revised: August 22, 2017
Accepted: March 21, 2018

DOI:
10.2174/1871520618666181029132017

Keywords: Anti-cancer drugs, nature-derived drugs, druglikeness, medicinal chemistry, phylogenetic distribution, target and pathway.

1. INTRODUCTION

Nature-derived drug contributes substantially to modern drug discovery [1-4]. Over one-third of the approved new molecular entities by U.S. Food and Drug Administration (FDA) from 1931 to 2013 are derived from or inspired by the natural products [5-8]. When it comes to the anti-cancer drugs approved in the past five years [9-13], the percentage of nature-derived drugs is even higher (as demonstrated in Table **1**, half of those drugs are derived from nature). With the emerging of automated separation coupling with structural analysis (like HPLC-NMR [14] and LC-MS/MS [15]), high-throughput screening [16-19], metabolic engineering [20-23], cheminformatics [24-30], and synthetic biology [31-34], discovery of anti-cancer drug from untapped natural resource is accelerated [35-37]. Moreover, a variety of computational methods have shown substantial ability to explore anti-cancer drug candidate [38-44]. These methods include computational polypharmacology [45], identification of synergistic anti-cancer drug combination by *in silico* approach [46], multi-tasking model for Quantitative Structure-Biological Effect Relationship (mtk-QSBER) simultaneously predict-ing pharmacological activities and ADMET properties [47-49], and so on. So far, a variety of nature-derived anti-cancer drugs are approved, like ingenol mebutate from *Euphorbia peplus* [50], trabect-edin from *Ecteinascidia turbinate* [51], homoharringtonine from *Cephalotaxus fortunei* [52] and romidepsin from *Chromobacterium violaceum* [53].

Despite the advances of those emerging technologies, several critical difficulties in discovering nature-derived anti-cancer drugs are still existed, including the challenge in selecting and resupply-ing of the drug-producing species [54], the complexity in identify-ing and isolating drug-like scaffold [55], the tough task of determin-ing cell-based biological activities [56], and so on. As illustrated in a pioneer and long-term study (across over 20 years) sponsored by the U.S. National Cancer Institute (NCI), over 35,000 species are randomly selected and screened *in vitro* and *in vivo* [57]. However, this work is eventually abandoned with few drugs discovered [57]. For the comprehensive discovery of anti-cancer drugs from all species on the planet, it would be much more chal-lenging to identify efficacious anti-cancer leads than the NCI's study as mentioned above [58]. Therefore, the "drug-productive clusters" in phylogenetic tree are proposed to narrow down the searching scope by only focusing on a much smaller amount of species within "cluster" [59], and this clustered pattern can facili-tate the discovery of new drug-producing species [59] and enable more prioritized and rational bioprospecting for the novel drug-like natural products [59, 60].

However, the way nature-derived anti-cancer drugs distribute in phylogenetic tree has not been studied so far, and it is oversimpli-

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1875-5992/19 $58.00+.00

Table 1. Nature-derived anti-cancer drugs approved by FDA in recent 5 years (2012-2016) [9-13].

Year of Approval	Drug Name	Indication	Source	Exemplar Species Origins	Reference
2012	Axitinib	Advanced RCC	S*/NM	*Zea mays*	*J. Med. Chem.*, **1996**, 39(12), 2285-92
	Bosutinib	CML	S*/NM	*Zea mays*	*Biochem. J.*, **1972**, 130(4), 901-11
	Cabozantinib	MTC	S*/NM	*Zea mays*	*PLoS One.*, **2012**, 7(7), e39782
	Carfilzomib	Multiple myeloma	ND	*Actinomycete strain*	*J. Antibiot.*, **1992**, 45(11), 1746-52
	Crizotinib	NSCLC	S*/NM	*Lentzea albida*	*Nat. Med.*, **1996**, 2(5), 561-6
	Enzalutamide	Prostate cancer	S/NM	*Homo sapiens*	*Drug Des. Devel. Ther.*, **2013**, 7, 875-81
	Homoharringtonine	CML	N	*Cephalotaxus fortune*	*J. Nat. Prod.*, **2016**, 79(3), 629-61
	Ingenol mebutate	Actinic keratosis	N	*Euphorbia peplus*	*Plant. Cell*, **2014**, 26(8), 3286-98
	Ponatinib	CML	S*/NM	*Lentzea albida*	*Nat. Med.*, **1996**, 2(5), 561-6
	Regorafenib	Metastatic CRC	S*/NM	*Lentzea albida*	*Nat. Med.*, **1996**, 2(5), 561-6
	Ziv-aflibercept	Metastatic CRC	B	*Homo sapiens*	*Mol. Cancer Ther.*, **2014**, 13(6), 1636-44
2013	Afatinib	Metastatic NSCLC	S*/NM	*Zea mays*	*J. Med. Chem.*, **1996**, 39(12), 2285-92
	Dabrafenib	Melanoma	S*/NM	*Zea mays*	*Biochem. J.*, **1972**, 130(4), 901-11
	Ibrutinib	MCL	S*/NM	*Zea mays*	*PLoS One.*, **2012**, 7(7), e39782
	Obinutuzumab	CLL	B	*Mus musculus*	*Blood*, **2015**, 125(12), 1901-9
	Trametinib	Melanoma	S*/NM	*Zea mays*	*J. Med. Chem.*, **1996**, 39(12), 2285-92
	Kadcyla	Breast cancer	ND	*Maytenus ovatus*	*J. Am. Chem. Soc.*, **1972**, 94(4), 1354-6
2014	Blinatumomab	B-ALL	B	*Mus musculus*	*J. Nat. Prod.*, **2016**, 79(3), 629-61
	Ceritinib	ALK-positive NSCLC	S/NM	*Zea mays*	*Biochem. J.*, **1972**, 130(4), 901-11
	Idelalisib	CLL, FL and SLL	S*/NM	*Zea mays*	*PLoS One.*, **2012**, 7(7), e39782
	Nivolumab	Melanoma	B	*Homo sapiens*	*Lancet Oncol.*, **2015**, 16(3), 257-65
	Pembrolizumab	Metastatic melanoma	B	*Mus musculus*	*N. Engl. J. Med.*, **2016**, 374(26), 2542-52
	Ramucirumab	Gastric cancer	B	*Homo sapiens*	*Cancer*, **2015**, 121(6), 883-92
	Siltuximab	MCD	B	*Homo sapiens*	*Clin. Cancer Res.*, **2015**, 21(5), 950-4
2015	Alectinib	NSCLC	S/NM	*Zea mays*	*J. Nat. Prod.*, **2016**, 79(3), 629-61
	Cobimetinib	Melanoma	S/NM	*Lentzea albida*	*Nat. Med.*, **1996**, 2(5), 561-6
	Daratumumab	Multiple myeloma	B	*Homo sapiens*	*J. Immunol.*, **2011**, 186(3), 1840-8
	Dinutuximab	Neuroblastoma	B	*Homo sapiens*	*Clin. Cancer Res.*, **2017**, 23(3), 804-813
	Elotuzumab	Multiple myeloma	B	*Homo sapiens*	*Mol. Cancer Ther.*, **2009**, 8(9), 2616-24
	Lenvatinib	Thyroid cancer	S/NM	*Zea mays*	*J. Med. Chem.*, **1996**, 39(12), 2285-92
	Necitumumab	NSCLC	B	*Homo sapiens*	*Lancet Oncol.*, **2015**, 16(3), 328-37
	Osimertinib	NSCLC	S/NM	*Zea mays*	*Biochem. J.*, **1972**, 130(4), 901-11
	Palbociclib	Breast cancer	S/NM	*Zea mays*	*PLoS One.*, **2012**, 7(7), e39782
	Imlygic	Melanoma	B	*Alpha-herpes virus*	*J. Clin. Oncol.*, **2015**, 33(25), 2780-8
	Lonsurf	CRC	ND	*Homo sapiens*	*Invest. New Drugs*, **2017**, 35(2), 189-197
2016	Atezolizumab	UCC	B	*Homo sapiens*	*Bioconjug. Chem.*, **2016**, 27(9), 2103-10
	Olaratumab	Soft tissue sarcoma	B	*Homo sapiens*	*Drugs*, 77(1), **2017**, 107-112

fied and challenging to just focus drug discovery on those "drug-productive clusters" [61], because the number of species in each cluster (from several hundred to even tens of thousands) is too large to be managed by the medicinal chemist of natural product [59, 62]. In particular, some drug-producing species (such as *Catharanthus roseus* [63]) yield multiple drugs and keep productive for a long period of time, while others (like *Streptomyces parvullus* [2]) remain yield free for several decades after their first drug [59, 64-66]. Thus, to discover a nature-derived anti-cancer drug, it is essential to distinguish those "consistently productive species" from less-productive ones based on multiple criteria, such as their phylogenetic distribution [64], the drug-likeness of their nature-derived drugs [1, 67] and their corresponding primary therapeutic target [59, 68-70]. Moreover, it is of great interest to conduct the above analyses on a comprehensive set of nature-derived drugs approved or marketed for cancer treatment.

In this study, 260 anti-cancer drugs approved in the past 70 years (1946-2016) were systematically collected and comprehensively reviewed. Firstly, all drugs were binned into 7 ten-year groups to analyze the discovery trends of anti-cancer drugs. Secondly, 207 drugs originated from 58 species were identified, and their species origins were divided into groups by their drug productivity. Thirdly, phylogenetic distributions of anti-cancer drugs were illustrated. Finally, species' productivity was statistically analyzed based on drugs' drug-likeness, therapeutic

targets and pathways. In sum, this study provided a comparative analysis of the species producing approved anti-cancer drugs, which may facilitate the discovery of novel therapeutics.

2. MATERIALS AND METHODS

2.1. Data Collection and Definition of Drug Type

260 Approved anti-cancer drugs were collected from the FDA official website (Drugs@FDA) and the seminal work of Newman and Cragg [2]. Species origins of all anti-cancer drugs were systematically identified based on another comprehensive analysis of the nature-derived drugs [59] and a further literature review conducted in this study. The primary therapeutic target of each anti-cancer drug was identified based on the information provided in *Therapeutic Target Database* (TTD) [4, 6, 8]. For a drug with multiple approval years, only the earliest approval year was accepted.

By following the same definition as the work of Newman and Cragg [2], all 260 studied drugs were classified into nine drug types (B, N, NB, ND, S*, S*/NM, S/NM, S and V). In particular, "B" referred to the biologics, peptide or protein drugs either isolated from an organism/cell line or produced by biotechnological means in a surrogate host; "N" described natural products; "NB" stood for natural botanical drugs; "ND" represented the drugs derived from a natural product, usually with semisynthetic modification; "NM" represented natural product mimics; "S*" was the abbreviation of drugs made by total synthesis based on the pharmacophore of natural product; "S" denoted the totally synthetic drug; and "V" was recognized as the vaccine drug.

2.2. Species Origins of Nature-Derived Anti-Cancer Drugs

Based on the previous studies [2, 59], 207 out of the 260 studied anti-cancer drugs were nature-derived. The species origin of each drug was identified by searching reputable literature using a combination of keywords: "drug name", "species", "natural product" and "nature". To further confirm drugs' species origin, a specific statement in the literature was needed (such as drug "originates from", "is derived from", "is isolated from" a species). For drugs derived from a natural product, drug-leads were searched first, followed by a search of host species as described above. Finally, the families of drugs' species origin, as well as all known species families in nature, were collected from the *NCBI taxonomy database* [62].

2.3. Species Categories Defined by Drug Productivity

Some drug-producing species yielded multiple drugs and kept productive for a relatively long period of time, while others remained yield free for several decades after their first drug [59, 64]. As shown in Table **S1**, the number of drugs approved in each ten-year binning group produced by those studied drug-producing species was listed, and all 58 species were therefore classified into three categories by their productivity of drugs: (1) the productive species yielding >2 drugs (CPS); (2) the newly emerging species producing drugs in recent 2 decades (CNS); (3) the less productive species with ≤2 drugs and yield free for recent 2 decades (CLS).

2.4. Illustrating Drugs' Distribution on Phylogenetic Tree

To illustrate the phylogenetic distribution of those studied 207 drugs, the phylogenetic tree on species family level was constructed using the automatic tree generator *iTOL* [71]. The name of species family was collected from the *NCBI taxonomy database* [62]. In the phylogenetic tree, drug-producing family and drug-productive cluster were colored and labeled, and the family names were provided at branch ends. Drug-producing family with CPS was colored in orange, and the families with only CNS or CLS were highlighted in green and blue, respectively. The outer layer of phylogenetic tree denoted the number of drug-producing species, which was colored according to their species category (orange, green and blue for CPS, CNS and CLS, respectively).

2.5. Calculating the Drug-like Properties

The physicochemical properties of the studied 207 drugs could be calculated using the *MODEL* [72]. Firstly, drug structures in SDF format were downloaded from the *TTD* [4, 6] and the *NCBI PubChem database* [73]. Five properties frequently used to reflect drug-likeness *via Lipinski rule of five* [74] were selected for evaluation, including drugs' molecular weight, cLogP, number of H-bond donors, number of H-bond acceptors and number of rotatable bonds. Moreover, two more properties frequently used to assess the drug-likeness (polar surface area [75] and number of heavy atoms [76]) were also included in the analysis of this study. Statistical difference was assessed by Student's *t-test*. The significant and moderate differences were shown by p-value <0.01 (**) and <0.05 (*), respectively.

3. RESULTS AND DISCUSSION

3.1. Developmental Trends of Anti-Cancer Drugs during the Past 70 Years (1946-2016)

In total, there were 260 anti-cancer drugs approved in the past 70 years. As shown in Fig. (**S1**), there was a clear rising trend in the number of approved anti-cancer drugs. In particular, the average number of approved drugs in the recent 30 years (~5.8 per year) was significantly higher than that approved before 1986 (~1.9 per year). The developmental trend of different drug types was illustrated in Fig. (**1**) and Fig. (**S2**) by binning them into 7 ten-year groups. The rising trend of approved anti-cancer drugs (orange) shown in Fig. (**1**) was clearer than that in Fig. (**S1**) with the recent 10 years as the climax of drug production (~8.5 per year). The number of approved natural products (N and NB) and that of approved drugs derived from nature (B, ND, S*, S*/NM, S/NM and V) were colored in green and blue, respectively (Fig. **1**). As shown, the nature-derived drugs constituted the major part of all approved anti-cancer drugs, and the approved natural products (green) played a constant role by contributing 0.34 anti-cancer drugs per year. Comparing with the approved natural products, the number of approved drugs derived from nature (shown in blue) increased significantly, which was the main driver of the rising trend of approved anti-cancer drugs (shown in orange). As shown in Fig. (**1**), the booming era of nature-derived drugs started from the middle of 1980s with a greatly increased number of biologics approved (especially antibodies [77] as shown in Fig. **S2**). In the recent 20 years, biologics still enjoyed a rapid growth, and the number of ND, S*, S*/NM and S/NM also increased substantially. This may come from the introduction of targeted therapy since the first discovery of Imatinib in 1996 [78].

3.2. Phylogenetic Distribution of Anti-Cancer Drugs

As shown in Table **S1**, there were 207 nature-derived anti-cancer drugs originating from 58 species, and the majority of these species (81%, in Table **2**) belonged to two species kingdoms (Bacteria and Viridiplantae). Many studied drugs were from species kingdom *Metazoa* with 84% originating from human. Therefore, the inclusion or exclusion of these drugs had a limited effect on our analysis. To study the phylogenetic distribution of those 207 studied anti-cancer drugs, 47 species within kingdoms of Bacteria and Viridiplantae were analyzed. As demonstrated in Table **S1**, these species were classified into three categories based on their productivity of drugs: (1) 11 productive species yielding >2 drugs (CPS); (2) 23 emerging species producing drugs in the recent 2 decades (CNS); and (3) 13 less productive species with ≤2 drugs and yield free for recent 2 decades (CLS). Phylogenetic distributions of anti-cancer drugs on species family level in Bacteria and Viridiplantae were illustrated in Fig. (**2**) and Fig. (**3**), respectively. As illustrated

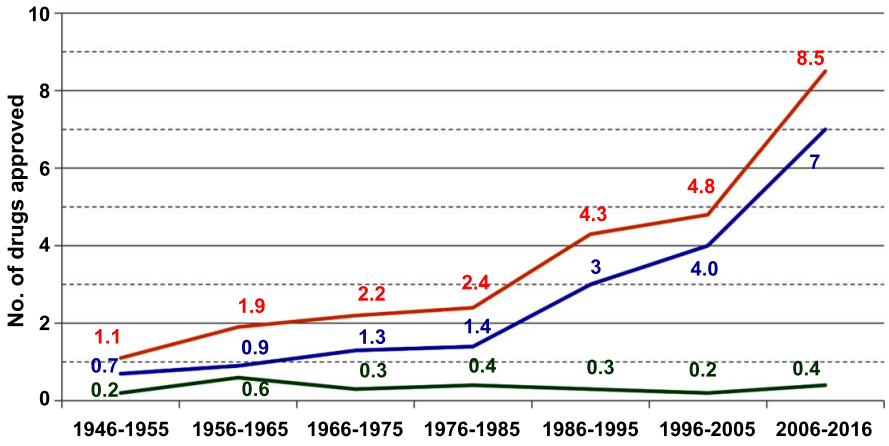

Fig. (1). The number of anti-cancer drugs (colored in orange), natural products (N and NB, colored in green) and drugs derived from nature (B, ND, S*, S*/NM, S/NM and V, colored in blue) approved in the past 70 years by binning drugs into 7 ten-year groups. Digital numbers denoted the number of drugs per year. (*The color version of the figure is available in the electronic copy of the article*).

Table 2. Distribution of 207 nature-derived anti-cancer drugs in different species kingdoms.

Kingdoms	Drug	Species	Family
Bacteria	45 (21.7%)	26 (44.8%)	10 (30.3%)
Viridiplantae	41 (19.8%)	21 (36.2%)	13 (39.4%)
Metazoa	120 (58.0%)	7 (12.1%)	6 (18.2%)
Others	4 (1.9%)	4 (6.9%)	4 (12.1%)

in Figure 2, Bacteria with 317 known families contained 9 drug-producing families, and 7 out of these 9 concentrated in 2 drug-productive clusters (*Actinonycetales* and *Gammaproteobacteria*). 2 drug-producing families with only CNS located outside these 2 clusters, but one of the families was in the previously identified clusters productive of drugs for all diseases [59]. *Viridiplantae* with 821 known families contained 13 drug-producing families (Fig. **3**) and 9 out of 13 located in 3 drug-productive clusters (*Commelinids*, *Fabids* and *Lamiids*). 4 remaining families were outside these 3 clusters, but 3 of them were in previous clusters productive of drugs for all diseases [59].

Statistical analysis further revealed that 87% and 67% of the approved anti-cancer drugs concentrated in 11 families producing multiple drugs and 5 drug-productive clusters, respectively (Table **3**), and the majority of CNSs located in clusters productive of anti-cancer drugs (Figs. **2** and **3**). Phylogenetic distribution of those studied drugs revealed that nature-derived anti-cancer drugs originated mostly from drug-productive families that tend to be clustered rather than scattered on phylogenetic tree. Comparing with the previous study [59], the number of clusters productive of anti-cancer drugs significantly decreased from 14 to 5, which was thus much easier to be managed by medicinal chemists of natural product. The clustered patterns of species origins of nature-derived anti-cancer drugs suggested that it is necessary to focus the bioprospecting effort on those specific families in the well-defined drug-productive clusters.

3.3. Discriminating the Druglikeness of Drugs Derived from CPSs and CLSs

Lipinski rule of five (RO5) was frequently used to assess the drug-likeness [74], which comprised 5 aspects of evaluation: molecular weight ≤500 Da, cLogP ≤5, No. H-bond acceptors ≤10, No. of H-bond donors ≤5, and No. of rotatable bonds ≤10. Moreover, 2 more physicochemical properties frequently used to assess the drug-likeness (polar surface area [75] and a number of heavy atoms [76]) were also included in this study. The number of nature-derived anti-cancer drugs with an available structure derived from CPSs, CLSs and CNSs was 56, 17 and 6, respectively. These 7 drug-like properties mentioned above were calculated using *MODEL* [72] and fully provided in Table **S2**. The statistical differences in these 7 properties among drugs from CPS, CLS and CNS were shown in Fig. (**4**) and Fig. (**S3**). As shown, there was statistical significance in 4 properties (cLogP, No. of H-bond donors, No. of H-bond acceptors and polar surface area, shown in Fig. **4**) between drugs from CPS and CLS, and the corresponding statistical differences (*p*-value between drugs from CPS and CLS) in molecular weight and No. of heavy atoms both equal to 0.07 (close to 0.05, shown in Fig. **S3**). Moreover, statistical significance was also observed between drugs from CNSs and CLSs (Fig. **4**), which revealed a much more similar drug-likeness between drugs from CPS and CNS than that between drugs from CLS and CNS. In other words, drugs from newly emerging species (CNS) shared similar drug-like properties to those from productive species (CPS), while the distinct difference between the drugs from CLS and CNS was observed. With the significant raise of drug approval standards and biomedical technologies [79-81], it might be reasonable to extrapolate that drugs from CLS were poor in drug-likeness properties if they were assessed by the latest approval standards. Thus, this finding suggested the researcher focus future bioprospecting on those species yielding multiple drugs and keeping productive for a long period of time, and it was necessary to assess, in advance, the drug-likeness of the secondary metabolites isolated from the aimed species, before this species was selected as a promising one for new drug discovery.

3.4. Therapeutic Targets of the Nature-Derived Anti-Cancer Drugs

The targets of 86 drugs from drug-producing species within the kingdoms of *Bacteria* and *Viridiplantae* were reviewed, and 77 out of these 86 were identified with primary therapeutic targets

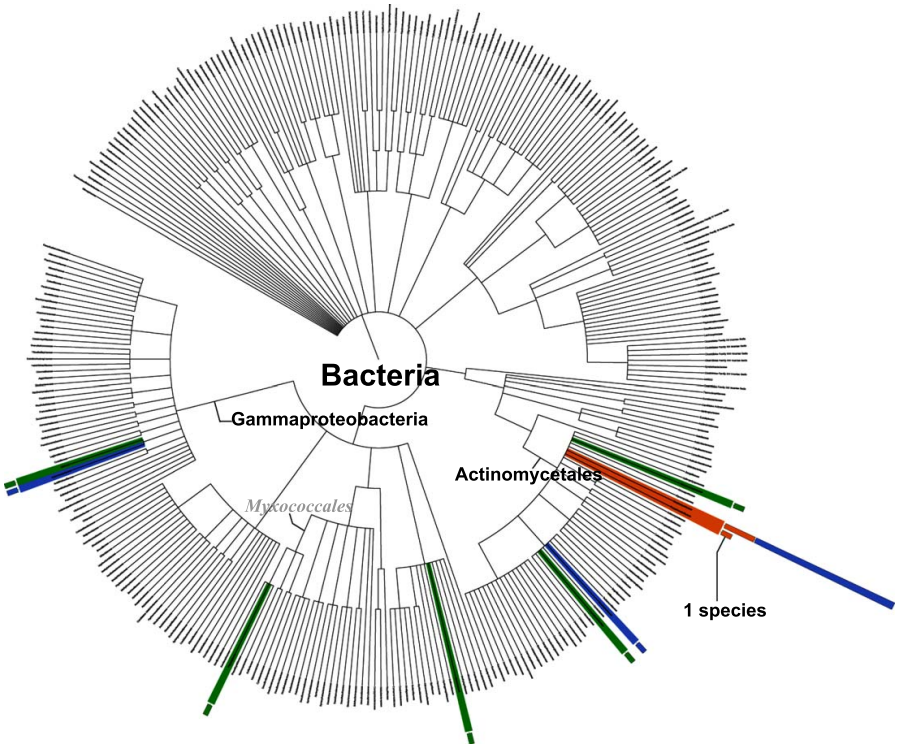

Fig. (2). Phylogenetic distribution of the studied drugs on the species family level in the *Bacteria* kingdom. Drug-producing family and drug-productive cluster were colored and labeled, respectively. The family name was provided at branch ends. Drug-producing family with CPS was colored in orange, and family with only CNS or CLS was colored in green and blue, respectively. The outer layer of the phylogenetic tree denoted the number of drug-productive species colored according to their species category (orange, green and blue for CPS, CNS and CLS, respectively). The cluster productive of anti-cancer drugs was defined as a relatively small branch of a phylogenetic tree with two or more drug-productive families (labeled in dark), while the previously identified clusters productive of drugs for all diseases [59] were labeled in grey. (*The color version of the figure is available in the electronic copy of the article*).

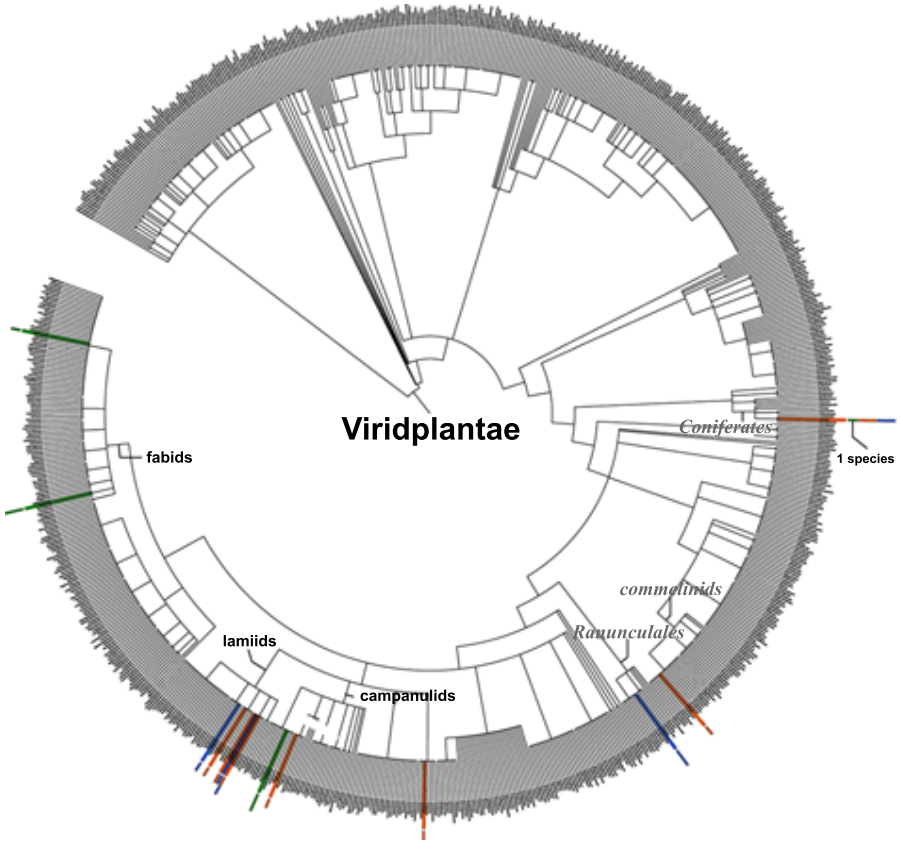

Fig. (3). Phylogenetic distribution of the studied drugs on the species family level in *Viridplantae* kingdom. The definition and explanation of all colors and labels were fully described in the legend of Fig. (**2**).

Table 3. Number of drugs in drug-producing families and drug-productive clusters. Those families producing multiple drugs were highlighted in bold.

Kingdom	Clusters Productive of Anti-Cancer Drugs	Drug-Producing Family	Category	No. of Drugs	Example of Drugs
Bacteria	Actinomycetales	*Streptomycetaceae*	CPS	25	Actinomycin D
		Pseudonocardiaceae	CPS	11	Imatinib
		Micromonosporaceae	CNS	1	Mylotarg
		Mycobacteriaceae	CLS	1	Mifamurtide
		Corynebacteriaceae	CNS	1	Ontak
	Gammaproteobacteria	*Enterobacteriaceae*	CLS	2	Asparaginase
		Pectobacteriaceae	CNS	1	Erwinaze
	--	*Neisseriaceae*	CNS	1	Romidepsin
	--	*Polyangiaceae*	CNS	1	Ixabepilone
Viridiplantae	Campanulids	*Apiaceae*	CPS	3	Alitretinoin
		Asteraceae	CNS	1	Arglabin
	Fabids	*Euphorbiaceae*	CNS	1	Ingenol mebutate
		Celastraceae	CNS	1	Kadcyla
	Lamiids	*Apocynaceae*	CPS	6	Vinblastine
		Icacinaceae	CPS	3	Belotecan
		Loganiaceae	CLS	1	Topotecan
		Rubiaceae	CPS	3	Elliptinium acetate
		Solanaceae	CLS	1	Solamargines
	--	*Poaceae*	CPS	19	Gefitinib
	--	*Taxaceae*	CPS	4	Paclitaxel
	--	*Cornaceae*	CPS	3	Irinotecan
	--	*Berberidaceae*	CLS	2	Etoposide

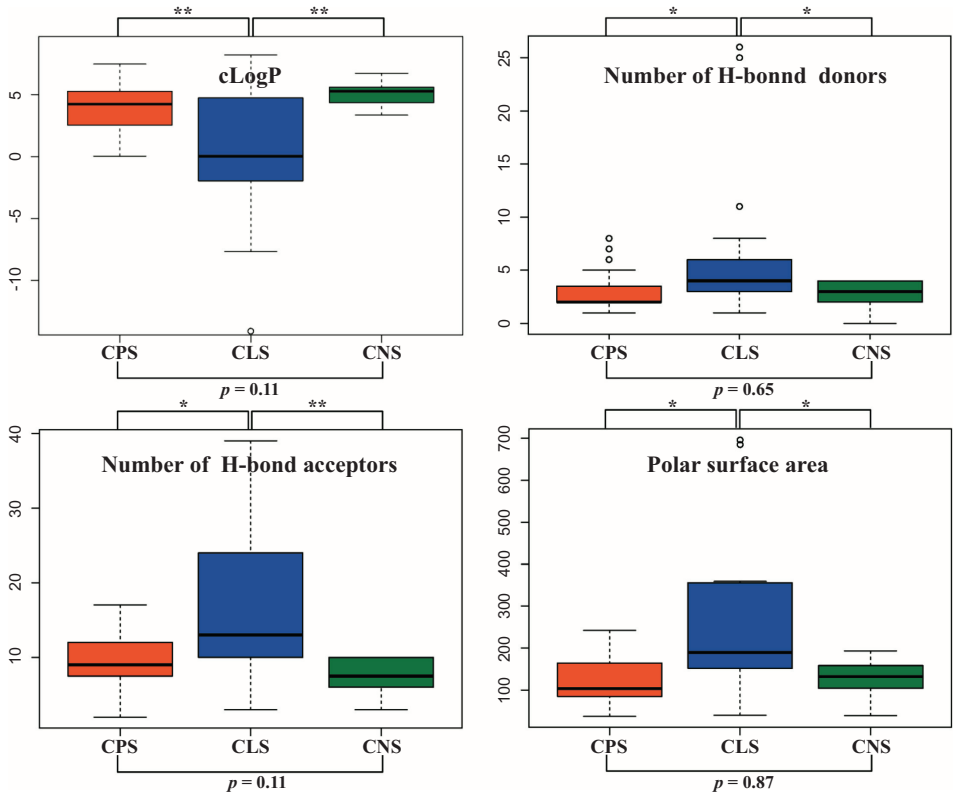

Fig. (4). Statistical differences in 4 drug-like properties (*cLogP*, *No. of H-bond donors*, *No. of H-bond acceptors* and *polar surface area*) among drugs from CPSs, CLSs and CNSs. Significant and moderate differences were shown by *p*-value ≤ 0.01 (**) and ≤ 0.05 (*), respectively.

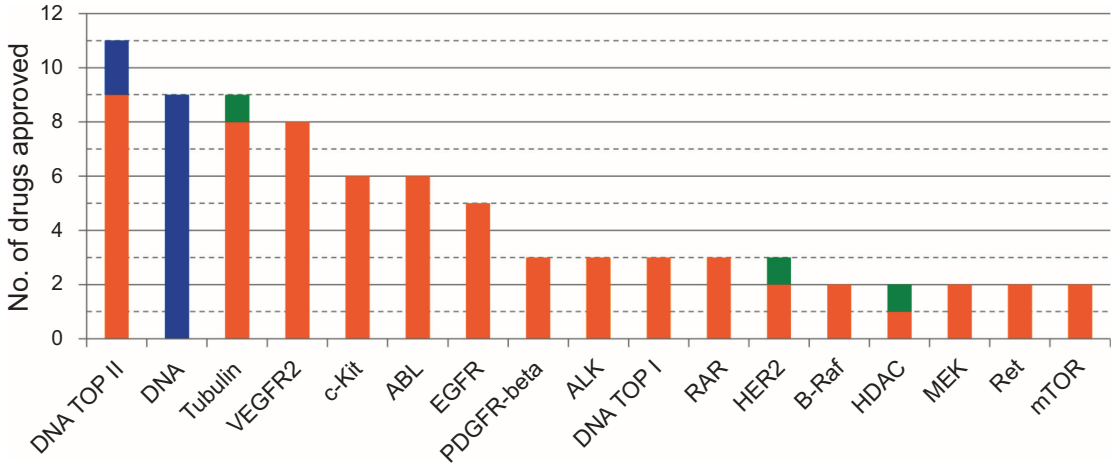

Fig. (5). The top-ranked therapeutic targets aimed by multiple anti-cancer drugs together with the number of their corresponding drugs. Drugs from CPS, CLS and CNS were in orange, blue and green, respectively. (*The color version of the figure is available in the electronic copy of the article*).

(the number of targets was 31 in total, shown in Table **S3**). These 31 targets were from several important target families such as kinase (52.7%), DNA related proteins and nucleic acids (24.7%), structural proteins (9.7%) and others (12.9%). As illustrated in Fig. (**5**), all drugs in CLS targeted DNA and DNA topoisomerase II, while drugs in CPS aimed at a much more diverse set of therapeutic targets (DNA topoisomerase II, VEGFR2, Tubulin, c-Kit and ABL were popular targets aimed by more than 5 anti-cancer drugs). There was a clear shift in drug targets from the previous DNA related molecules to the current kinase proteins.

3.5. Pathways Affiliated by the Nature-Derived Anti-Cancer Drugs

Pathways affiliated by 86 drugs from drug-producing species in *Bacteria* and *Viridiplantae* were also studied. 72 out of these 86 were identified as affiliated with at least one KEGG pathway [82], and these drugs aimed at 28 primary therapeutic targets (the total number of pathways was 22, shown in Table **S4**). The top-ranked pathways affiliated by a large number of drugs (≥5) were illustrated in Fig. (**S4**). As shown, drugs from CLS affiliated with *DNA replication, transcription pathway* and *MAPK pathway*, while drugs from CPS aimed at not only the same pathways as that from CLS but also several other diverse and popular pathways, including *ErbB pathway*, *Ras pathway*, *tight and gap junction*, *PI3K-Akt pathway*, *VEGF pathway*, *mTOR pathway*. It was clear (Fig. **S4**) that *DNA replication, transcription pathway* and *MAPK pathway* were crucial for the discovery of anti-cancer drug from both CLS and CPS. However, current new drug exploration was gradually shifted to those pathways enriched by kinase proteins (such as EGFR, ABL, VEGFR2, and so on).

CONCLUSION

Our work revealed that nature-derived anti-cancer drugs originated mostly from drug-productive families that tend to be clustered rather than scattered on the phylogenetic tree. A significant difference in drug-likeness between drugs from CPS and CLS was observed, and drugs from CNS shared similar drug-like properties to those from CPS, which indicated a significant improvement in drug-likeness for the current discovery of anti-cancer drugs. These findings suggested the researchers focus bioprospecting efforts on species yielding multiple drugs and keeping productive for long period of time, and it was necessary to assess, in advance, drug-likeness of the secondary metabolites isolated from the aimed species, before this species was selected for new drug discovery.

LIST OF ABBREVIATIONS

ALK	=	Anaplastic Lymphoma Kinase
B-ALL	=	B-cell Acute Lymphoblastic Leukemia
CLL	=	Chronic Lymphocytic Leukemia
CML	=	Chronic Myelogenous Leukemia
CRC	=	Colorectal Cancer
EGFR	=	Epidermal Growth Factor Receptor
FL	=	Follicular Lymphoma
HDAC	=	Histone Deacetylase
HER2	=	Epidermal Growth Factor Receptor 2
MCD	=	Multicentric Castleman Disease
MEK	=	Mitogen-activated Protein Kinase Kinase
MTC	=	Medullary Thyroid Cancer
mTOR	=	Mammalian Target of Rapamycin
NSCLC	=	Non-small Cell Lung Cancer
PDGFR	=	Platelet-Derived Growth Factor Receptor
RAR	=	Retinoic Acid Receptor
RCC	=	Renal Cell Carcinoma
SLL	=	Small Lymphocytic Lymphoma
TOP	=	Topoisomerase

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are the basis of this research.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

The National Natural Science Foundation of China (81872798), National Key Research and Development Program of China (2018YFC0910500), the Innovation Project on Industrial Generic Key Technologies of Chongqing (cstc2015zdcy-ztzx120003), and the Fundamental Research Funds for the Central Universities (2018QNA7023, 10611CDJXZ238826, 2018CDQYSG0007, CDJZR14468801, CDJKXB14011).

SUPPLEMENTARY MATERIAL

Supplementary material is available and downloadable from the official website of ACAMC.

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