CURRENT TRENDS IN ANTICANCER DRUG PROTOTYPE *IN VITRO* PHARMACOLOGY: BIBLIOMETRIC ANALYSIS 2019–2021

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Identification of novel low molecular weight compounds with antitumor activity is the first important step towards the development of candidate drugs and a popular trend in *in vitro* pharmacology. The aim of the study was to assess the key trends and rank the scientific priorities in anticancer drug design using bibliometric analysis. The protocol involved using the panel of bibliographic databases (PubMed, Scopus, Cortellis) and analytical web-based tools PubChem, FACTA +, ClustVis, Reaxys, PathwayStudio and VOSviewer software to review a sample of 1657 papers issued 2020–2021.The work was also focused on 70 new promising basic structures and derivatives targeted at inhibiting both individual pro-tumor proteins and signaling cascades. It was found that serine-threonine protein kinases, receptor tyrosine kinases, DNA topoisomerases and tubulins as well as signaling pathways PI3K, mTOR, AKT1, STAT3, HIF-1a, and p53 account for up to 60% of the total structure of cellular targets for the design of anticancer drugs. The increasing scientific interest in innovative inhibitors of tumor-associated protein complexes, transcription factors and metabolic enzymes has been found. The compounds, which belong to heterocycles, glycosides, quinones and terpenes, were mentioned in 71% of papers as the basic structures for antitumor derivatives design. Papers, published in 2019, in which the compounds, such as lapachone, luteolin, quercetin, monastrol, and crisosplenol D are studied in the context of the design of new drug prototypes, have the highest citation rate. The systematic bibliometric approach involving the use of a panel of analytical resources makes it possible to assess R&D trends and scientific priorities in anticancer drug design, thus organically complementing the classic reviews in periodicals.

Keywords: cancer, drugs, pharmacology, bibliometric analysis, publication activity, protein target

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СОВРЕМЕННЫЕ ТЕНДЕНЦИИ *IN VITRO* ФАРМАКОЛОГИИ ПРОТОТИПОВ ПРОТИВООПУХОЛЕВЫХ ЛЕКАРСТВ: БИБЛИОМЕТРИЧЕСКИЙ АНАЛИЗ ЗА 2020–2021 ГГ.

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Выявление новых низкомолекулярных соединений, обладающих противоопухолевой активностью, является первым важным шагом на пути создания кандидатных лекарств и популярным направлением в *in vitro* фармакологии. Целью исследования было оценить ключевые тенденции и ранжировать научные приоритеты в области дизайна противоопухолевых лекарств с применением библиометрического анализа. Протокол предполагал использование панели библиографических баз данных (PubMed, Scopus, Cortellis) и аналитических ресурсов PubChem, FACTA+, ClustVis, Reaxys, PathwayStudio и VOSviewer для исследования выборки из 1657 публикаций за 2020–2021 гг. В работе также систематизирован материал по 70 новым перспективным производным на основе базовых химических структур, нацеленных на ингибирование отдельных про-опухолевых белковых молекул и сигнальных каскадов. Установлено, что серин-треониновые протеинкиназы, рецепторные тирозинкиназы, ДНК-топоизомеразы и тубулины, а также сигнальные пути PI3K, mTOR, AKT1, STAT3, HIF-1a и p53 составляют до 60% в общей структуре клеточных мишеней для дизайна противоопухолевых лекарств. Отмечен рост научного интереса к инновационным ингибиторам опухоль-ассоциированных белковых комплексов, факторов транскрипции и метаболических ферментов. Соединения из класса гетероциклов, гликозидов, хинонов и терпенов в 71% работ служат базовыми структурами для дизайна противоопухолевых производных. Лидирующие позиции по цитированию занимают вышедшие в 2019 г. публикации, в которых рассмотрены такие соединения, как лапахон, лютеолин, кверцетин, монастрол и кризосленол D, в контексте дизайна новых прототипов лекарств. Системный библиометрический подход с использованием панели аналитических ресурсов позволяет оценить тенденции в области разработки и дизайна противоопухолевых лекарств и выявить приоритеты научного интереса, органично дополняя классические обзорные работы в периодических изданиях.

Ключевые слова: рак, лекарства, фармакология, библиометрический анализ, публикационная активность, белковые мишени

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Progress in the therapy of socially significant diseases, including malignant neoplasms (MN), is organically linked to success in research and development (R&D) of the new drug prototypes, the pharmacologically active molecules, having the greatest antitumor effect and maximum conformity of physical and chemical parameters to canonical drug-like structures [1]. One of the evidence-based approaches to the drug discovery consists in design of molecules, which possess the desired properties and affect the cancer-related proteins [2–4]. Defining the mechanism of action of anticancer drug prototypes and the whole range of on-target and off-target proteins is essential for design of the highly selective drugs with minimal side effects. The development of the improved anticancer drugs follows from the properties of the tumor itself: intertumor and intratumor heterogeneity, and the diversity of mechanisms for resistance [5]. On the other hand, many pharmacotherapeutic approaches require improving the benefit–harm balance, since many existing anticancer drugs can cause severe side effects [6].

The number of annual publications dedicated to identification of the novel peptide and non-peptide molecules with anticancer activity, repositioning effects and prescriptions, is about 2700–3400 (over the five-year period, according to

PubMed (accession on May 20, 2021). It should be noted that the review papers are focused mostly on systematizing the data on the anticancer drug prototypes, either belonging to a certain chemical taxon, or a spectrum of synthesized derivatives with the same chemical scaffold. Papers are also focused on discussing the range of biologically active substances with respect to the only molecular target. Nevertheless, reviews are a major source of scientific analysis in describing the current trends in drug discovery. Thus, the works [7, 8] cover the actual cancer-associated molecular targets, assessment of biological effects and concepts of the drug design, which in recent years has been intrinsically linked to computer-aided modeling (QSAR and others) [9]. At the same time, the search for current trends in drug prototypes, together with the interpretation of medical and biological effects of various anticancer compounds, results in the need for prompt data analysis from the multiple literature and biomedical sources. When performing without the use of customized algorithms and automated methods of data extraction (known as text mining), such an analysis can be very time-consuming. However, the application of the bibliometric analysis with adapted algorithms for creating an up-to-date "analytical portrait", which includes a more diversified repertoire of research data on drug prototypes and their molecular targets, has proved to be effective in defining the current trends in molecular oncology and pharmacology [10–13]. The aim of the study was to assess the key trends and rank the scientific priorities in anticancer drug design using bibliometric analysis.

METHODS

PubMed (https://pubmed.ncbi.nlm.nih.gov/) was used to search for journal papers (issued from May 20, 2020 to May 19, 2021) by keywords “antitumor and anticancer activity”. Inclusion criteria was “original research” reporting the new data on identification of anticancer drug prototypes and the best relevancy of search. Exclusion criteria was paper types “Books and Documents”, “Clinical Trial”, “Meta-Analysis”, “Randomized Controlled Trial”, “Review” and “Systematic Review”. A total of 1902 papers were found, from which 240 reviews and five clinical trials were subsequently excluded. 402 papers were selected from the remaining 1657 experimental papers, based on the abstracts analysis, and included in the target sample.

VOSviewer software [14] was used for keyword co-occurrence analysis in the papers from the target sample, as well as for keyword frequency analysis of MeSH terms and authors’ terms in the papers' abstracts.

Names of low molecular weight non-peptide compounds were extracted from papers' abstracts and keyword listings. Their MeSH classification groups (Classification/Ontologie/MeSH-Tree) were defined using PubChem database (https://pubchem.ncbi.nlm.nih.gov/).

Analysis of research trends and publication activity over the five-year period (2016–2020) was performed using the Scopus database (https://www.scopus.com/) (Elsevier; Netherlands). The key “compound name and tumor” (for example, “magnolol and tumor”)was used as a search query. The scientific interest to papers, issued in 2019, was assessed by the total number of citations for papers issued before May 19, 2021, being corrected for self-citation of all co-authors of the paper. Another parameter was the average number of citations per paper, issued in 2019.

Associations between protein targets, their cancer significance and drug prototypes were analyzed using the Pathway Studio and Reaxys (Elsevier; Netherlands). These resources enable extracting the links between different molecular entities from biomedical data containing in twenty million abstracts and several million full-text papers with the help of Medscan software. They adapted for comprehensive search and prediction of drug targets as well as constructing of signaling pathways from the internal curated database. Associations found between molecular targets and key biological processes as “malignant transformation” and “cancer progression” was used to create the interaction map.

Web-based tool FACTA+ v.0.9 (accession on June 29, 2019) (http://www.nactem.ac.uk/facta/) was used to find biomedical associations in the full-text papers of the MEDLINE database.

Cortellis database (https://www.cortellis.com/intelligence) (Clarivate Analytics; UK) was used for patent search.

Principal component analysis (PCA) using k-means clustering and creating a heat map were performed using the ClustVis web-base tool [15]. The singular values decomposition method with imputation was used for PCA. It allows to generate and visualize the numeric data set geometric structure while imputing the missing values (imputation). Data preprocessing options included the following options: data transformation – “no transformation”; row scaling — “no scaling”. The heat map options were as follows: cluster distance for rows and columns — Pearson correlation or “correlation”, clustering method for rows and columns — “average”.

RESULTS

Analysis of abstracts from the target sample (402 papers) made it possible to define distribution of the occurrence frequency for keywords, which were related to identification of anticancer drug prototype and were mentioned in the text massive more than 10 times (Fig. 1). Fig. 1 allows one to see the focus in studying the pharmacological targeting of signaling pathways involving RAC-α serine/threonine-protein kinase (AKT1), signal transducer and activator of transcription (STAT)-3, hypoxia-inducible factor 1-α (HIF-1α), and p53-dependent pathways. Cancer-associated protein targets can be also distinguished: protein kinases (PKC and AMPK), tubulin, matrix metalloproteinases (MMP), poly (ADP-ribose) polymerase 1 (PARP1), epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGFR). Furthermore, targeting of caspases, aimed at activation of apoptotic programs in tumor cells, provides another important field of research.

Visual representation of keyword co-occurrence, mentioned in more than three papers, is provided in Fig. 2. The figure presents five clusters with semantic links between the keywords. Thus, the pronounced co-occurrence was observed in the following keywords pairs: histone deacetylase–quinolines, topoisomerase inhibitors–indoles (or pyrazoles, or pyrimidines), tubulin modulators–chalcones (or naphthalenes). Thus, the analysis of papers abstracts and keyword co-occurrence (Fig. 1 and 2) made it possible to identify the studies focused on the design of chalcone and licochalcone (flavonoids with opened pyran ring), naphthalene, saponin, indole, quinolone, sesquiterpene, pyrazole, pyridine (pyrimidine), steroid, curcumin and britanin derivatives exhibiting anticancer activity. It is interesting to note that a sufficient number of papers were focused in the design optimization of tubulin polymerization inhibitors [16]. According to 10-year PubMed statistics, the number of new studies in this field remained stable, with a slight decline, observed in 2019–2020, which could demonstrate the decrease in scientific interest. Fig. 1 and 2 also show that

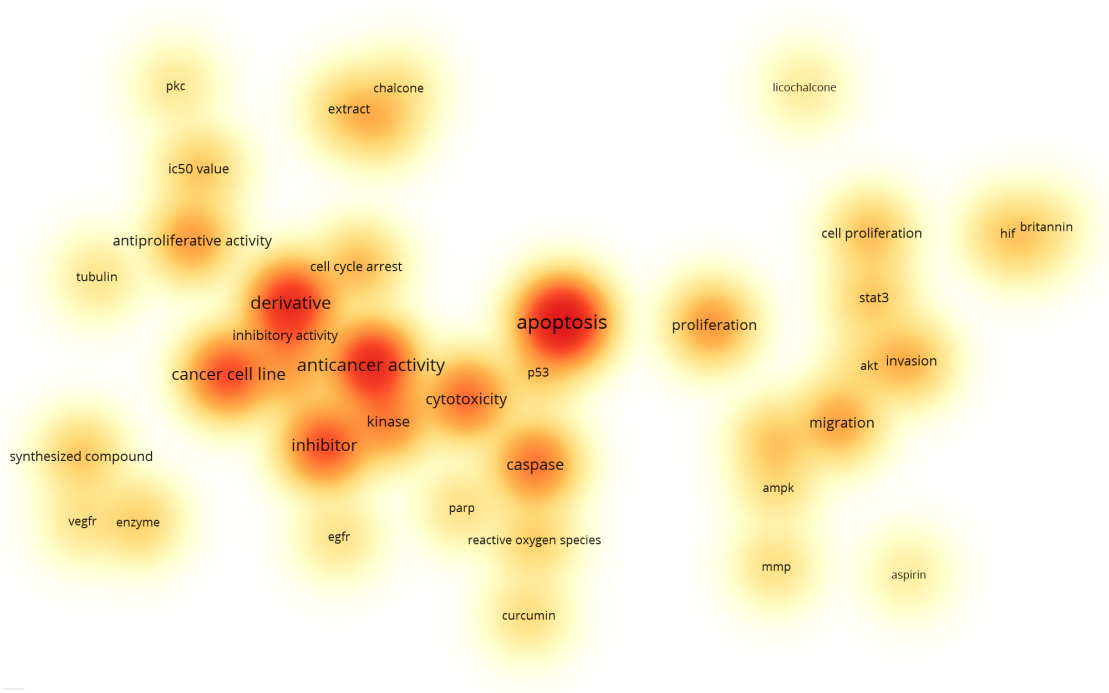

Fig. 1. Heat map of keyword (MeSH terms and authors' terms) mention frequency in the paper's abstracts

immortalized human embryonic kidney cell line HEK293, human colorectal carcinoma cell line HCT116, human lung carcinoma cell line A549, and mammary duct adenocarcinoma cell line (MCF-7) have become prevalent *in vitro* model systems. These were used for phenotype screening aimed at investigation of biological activity of novel drug prototypes, obtained by organic synthesis or extracted from plants, marine algae and fungi. Many medicinal plants are used in ethnopharmacology, for example, in China, which has provided the basis for the contribution of this country researchers from to the publication activities.

Fig. 3 demonstrates that compounds, representing the classes of heterocycles, glycosides, quinones and terpenes, appear to be the most abundant (71%) in the pool of all chemicals. Attention should be drawn to the terpenes and terpenoids, which is of high scientific priority and is considered an active "donor" of basic structures for synthesis of anticancer drug prototypes [17]. Furthermore, assessing the occurrence frequency of compound names in the papers' abstracts showed that it was possible to distinguish at least 29 most popular chemical structures (acridine, anthraquinone, dibenzyl,

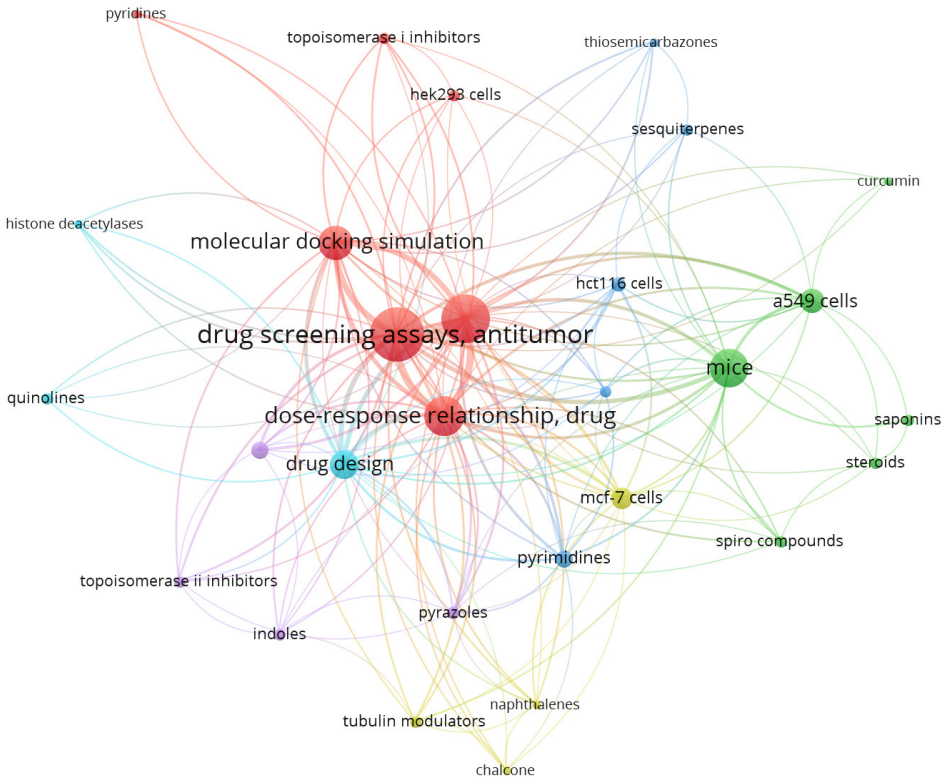

Fig. 2. Distribution of keyword (MeSH terms and authors' terms) co-occurrence based on the bibliographic data analysis

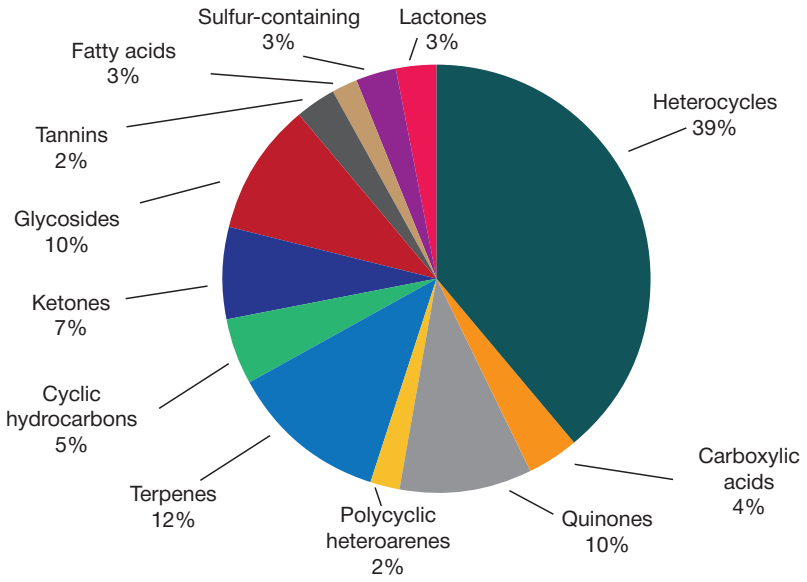

Fig. 3. The distribution of major groups of non-peptide organic compounds as new anticancer drug prototypes

stilbene, phenanthridine, pyranocarbazole, benzopyran, imidazolo-pyridine, indole, indolizine, naphthyridine, phthalazine, chinazoline) used for organic synthesis of new derivatives with anticancer activity and other spectrum [18, 19]. Thus, indole, quinazoline, acridine and pyridine derivatives in total account for 35% of all ones.

The trends of publication activity over the 5-year period (2016–2020) performed for 150 compounds, including the names of synthetic (46%) and natural (54%) chemical scaffolds, is presented in Fig. 4. It is reasonable to distinguish a discrete group of compounds (for example, derivatives of 1,6-naphthypyridone, sulfonylazaspirodienone, N-acyl-o-phenylenediamine and scabioside C), in which the anticancer activity was found for the first time. Fig. 4 also shows the re-emerging scientific interest in dioscin, cinnoline, indolizine, nargenicin A1 derivatives and quercetin. It follows from the growing number of publications, issued in 2020, describing the new anticancer effects for these compounds. On the other

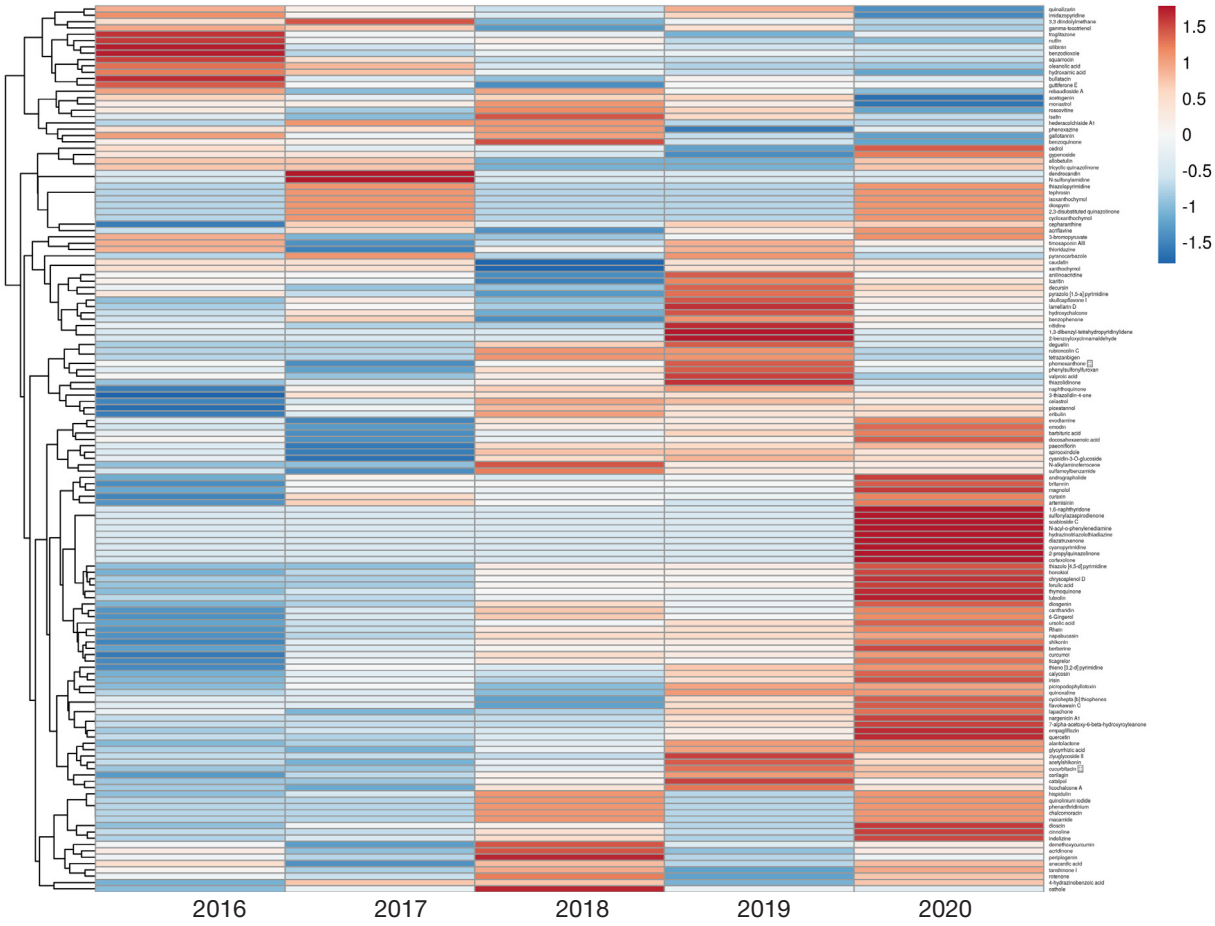

Fig. 4. Heat map of changes in publication activities (2016–2020) on identifying the new anticancer drug prototypes. Note: legend scale — cluster distance; decrease and increase in the number of papers are highlighted in red and blue colors, respectively

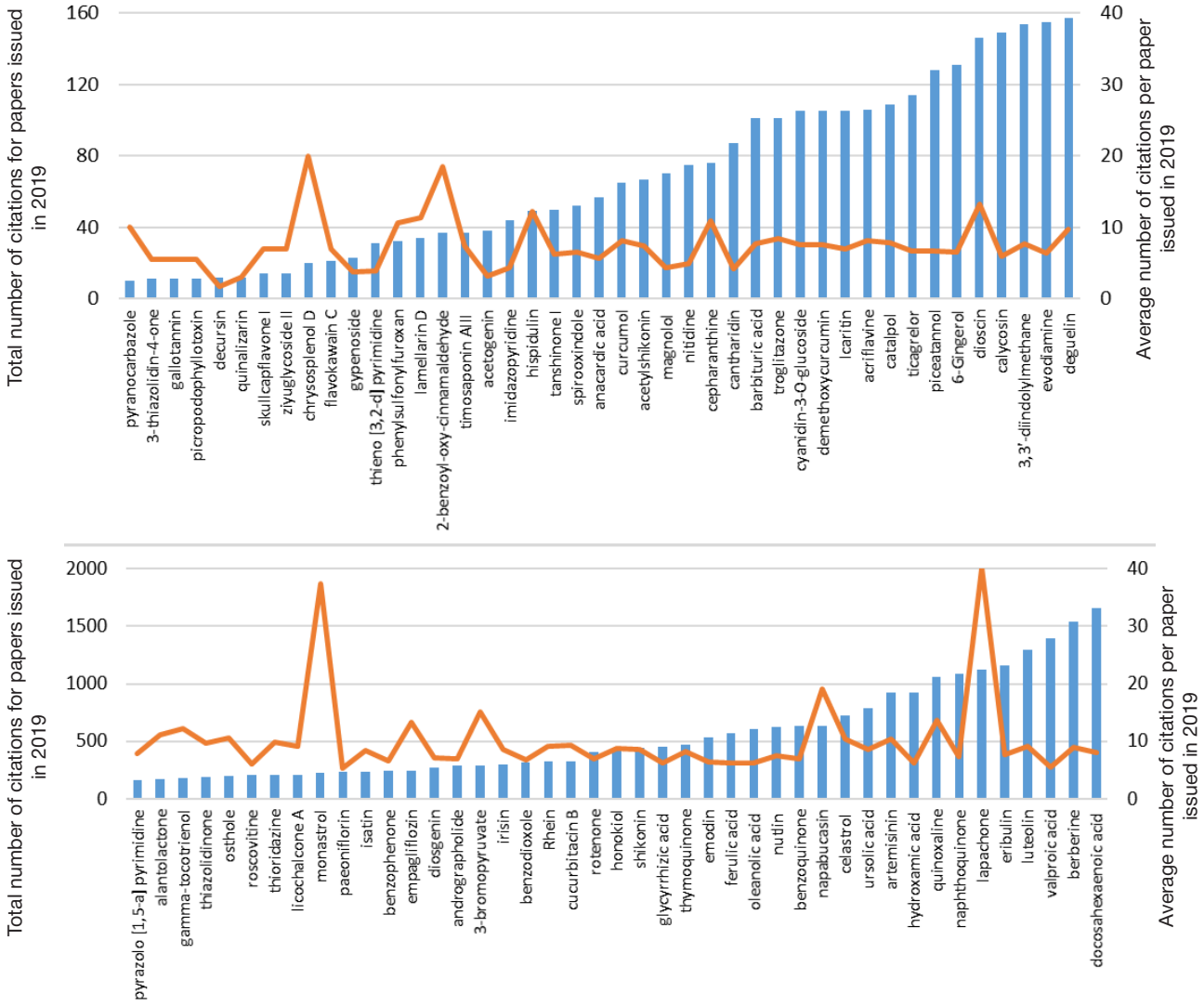

Fig. 5. Citations of papers issued in 2019 and focused on the anticancer drug prototype identification. Original names of compounds are provided

hand, publication activity with a reference to derivatives of thiazolidinedione (troglitazone), nutlin, silybin, squamocin, and derivatives of benzodioxole, oleanolic acid, and hydroxamic acid declined gradually in 2018–2020 compared to 2016–2017 period.

In addition to assessment of dynamic changes in the papers number, citing the papers, issued in 2019, was also analyzed. Fig. 5 shows that, citation rate in 2019–2021 (minimum threshold: 1000 citations) was observed for studies reffering quinoxaline, naphthoquinone, berberine, valproic acid and docosahexaenoic acid derivatives, as well as on lapachone, luteolin and quercetin. The latter is the "cite leader", which is mentioned 4200 times. However, based on the average number of citations per paper, issued in 2019, (minimum threshold: 15 citations), publications referring to crisosplenol D, 2-benzoyl-oxy-cinnamaldehyde, monastrol and lapachone ranked first in the context of new anticancer drug prototypes development.

The effective anticancer drug design is intrinsically linked with the related biomedical area of identifying the molecular targets. Efforts in this complementary area involve identification of mechanisms of action of drugs, which is critically important for differentiation of their on-target and off-target effects, as well as for design of highly selective compounds affecting the desired range of molecular targets. The vast majority of the clinically significant targets are the monomeric proteins or, more rarely, the oligomeric protein complexes [20]. Thus, the search for protein targets for a number of the priority anticancer drug prototypes (Fig. 5), contained in the Reaxys database, has helped to find out molecular targets has been mapped for the other three compounds, except crisosplenol D. As it turns out, the 2-benzoyloxycinnamaldehyde structure similar, ((E)2-(3-oxoprop-1-en-1-yl) phenyl benzoate), inhibits cyclin-dependent kinase 4, CDK4 (Target ID: 820056979) enzymatic activity, glutathione reductase (Target ID: 820106479) and farnesyltransferase (Target ID: 470858527). However, the monastrol and lapachone derivatives exhibit more optimal drug-like properties (compliance with the "rule of five" parameters [21]) compared to 2-benzoyl-oxy-cinnamaldehyde, and have a greater potential for identification of their molecular target. Reaxys database contains 31 and 117 records (accession on May 29, 2021) about the monastrol and lapachone targets, respectively. Among them, it can be found Aurora A protein kinase (Reaxys Target ID:818366617), M-phase inducer phosphatase 2 (Target ID: 820046846), DNA topoisomerase I (Target ID: 818289566), DNA topoisomerase II (Target ID: 824645880), glutathione S-transferase P (Target ID: 820104166), K-Ras GTPase variants (Target ID: 819104337) with G12C and Q61R substitutions, NAD(P)H quinone dehydrogenase 1 (Target ID: 820009294).

In Table, the new experimental synthetic and natural compounds, exhibiting anticancer activity [22–92] were shown with respect to molecular target mapping and the mechanisms

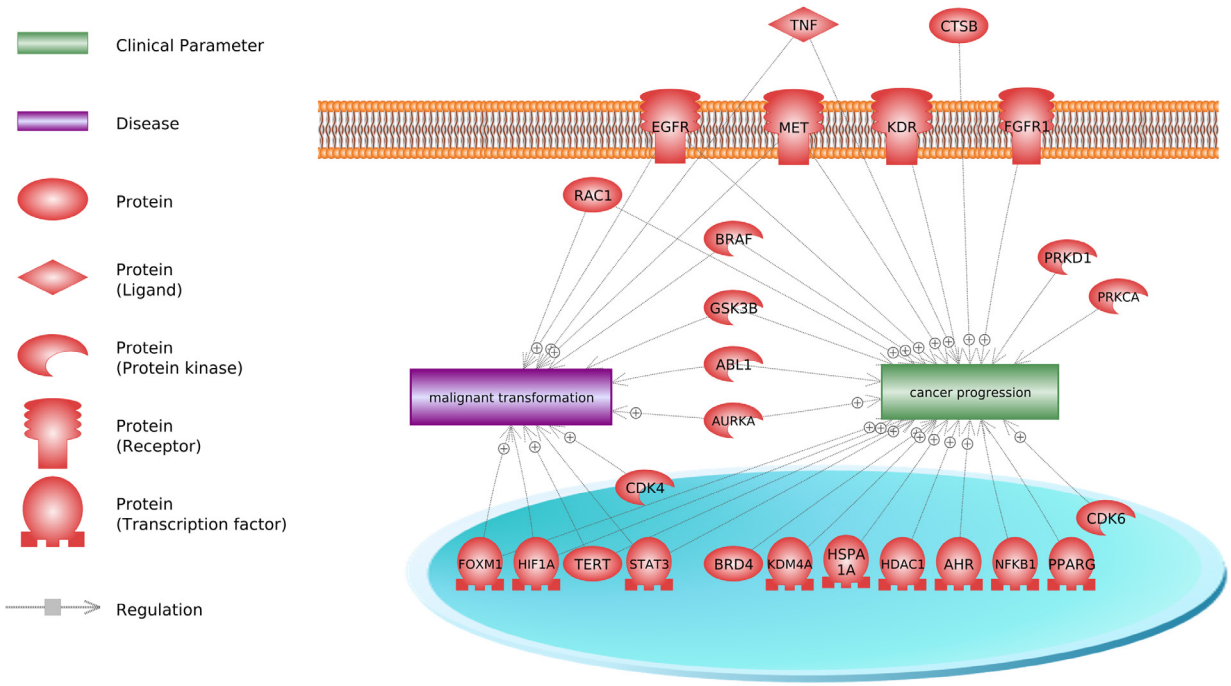

Fig. 6. Associations between the protein targets of anticancer drug prototypes returned by the queries "malignant transformation" and "cancer progression" in the Pathway Studio

of action studies. Scientific interest in such compounds follows from increased citation numbers and existence of patent potential. Furthermore, the newly identified chemical scaffolds, exhibiting a broad spectrum of anticancer activity, may later be used for design and synthesis of their derivatives. It is worth noting that papers on drug target mapping currently represent the great scintific demand and have a high citation rate in experimental pharmacology area.

DISCUSSION

Analysis of data presented in Table revealed the following quantitative distribution of the new anticancer drug protein targets: protein kinases (38%), DNA topoisomerases I and II (10%), transcription factors (9%), clinically significant protein-protein complexes (7%), cytoskeleton proteins (tubulin) (5%), and, finally, the rest of the diverse targets' group accounted for 40%. It is noteworthy that the latter group included phosphodiesterase 5A (PDE5A), Na+-glucose cotransporter 2 (SGLT2), and glutathione S-transferase (GSTP1) and dihydrofolate reductase (DHFR) enzymes, associated with chemotherapy drug metabolism and involved in the drug-resistant tumor phenotype formation [93]. Therefore, blockade of such enzymes may be considered a complementary pharmacological strategy, enabling to decrease chemoresistance. Analysis of papers' abstracts made it possible to determine the mechanism of action of anticancer drug prototypes (Table) which represent, mainly, competitive or noncompetitive reversible inhibition of the enzymes' catalytic activity.

Table demonstrates scientific interest in low molecular weight compounds that capable of modulating the function of transcription factors (for example, HIF-1a, FOXM1, ATF4). This is a group of intracellular nuclear proteins, which have been considered the extremely complicated molecular objects for drug design for a long time [94]. The search for new compounds disturbing signal transduction in the classic cancer-associated signaling pathways remains the traditional approach for carcinogenesis inhibition. Based on bibliometric analysis over 2020–2021, it should be pointed out that references to the PI3K, mTOR, AKT1, STAT3, HIF-1a and p53 signaling cascades were most often found among the pharmacologically targeted signaling pathways.

One more group can be seen in Table, including the compounds (LQFM126, E7386, britanin) and miconazole, which have the potential to selectively modulate the protein complex affinity. This approach to drug prototype design is innovative, since it is based on the pharmacological targeting of conservative interfaces of protein-protein interactions (PPI) with low mutation rate [95, 96]. However, there is a number of polemical papers [97, 98], reporting the opposite, namely, predominant accumulation of mutations, associated with carcinogenesis, in the PPI interfaces of clinically significant protein complexes. This point is needed for in-depth study of the mutation factors' significance for drug targeted protein interfaces.

Then, we searched for information of involvement in carcinohenesis of the protein targets (listed in Table) using Pathway Studio. The assessment was performed based on the presence of links between proteins, and terms "malignant transformation" and "cancer progression". The results were selected on the availability of at least five papers, reporting the association of each protein target with each of these parameters. Thus, the visualization (Fig. 6) has revealed many evidence on the cancer involvement of majority of protein targets (Table).

The table also demonstrates that, on the one hand, STAT3 has been identified as a new protein target for the well-known anticancer drug napabucasin. On the other hand, studying the repositioning effects of miconazole, troglitazone, dexamethasone, vinpocetine and empagliflozin has made it possible to determine one more type of their biological activity, that is the anticancer activity. It can be assumed that such activity results from the modulating of signal transduction in the pro-oncogene pathways.

Pathway Studio can help to found out that the main type of interaction between the protein targets, was a post-translational modification by means of phosphorylation. The identified binary protein-protein interactions, where the first protein of a pair phosphorylates the second protein, are as follows: EGFR/STAT3, MET/STAT3, GSK3B/HIF1A, ABL1/

Table. Relationship between the biological activity of new anticancer drug prototypes and their molecular targets

Biologically active compound	Description	Source
Protein targets		
LQFM126	PPI* inhibitor between MDM2 and p53	[22]
E7386	PPI inhibitor between β-catenin and CREB	[23]
Britanin	PPI inhibitor between HIF-1α and Myc	[24]
*Miconazole**	PPI inhibitor between DDIAS and STAT3	[25]
5F-203	Activator of aryl hydrocarbon receptor (AHR)	[26]
Emodin	Activator of AHR	[27]
3/4-(pyrimidin-2-ylamino) benzoyl)-based hydrazine-1-carboxamide/carbothioamide derivatives	Antagonist of retinoic acid receptor α (RXRα)	[28]
Epigallocatechin and podophyllotoxin conjugates (epigallocatechin-3-gallate-4β-triazolopodophyllotoxin)	Inhibitor of DNA topoisomerase II (TOP2)	[29]
Tricyclic quinazolinone derivatives	Inhibitor of DNA topoisomerase I (TOP1)	[30]
5(or 6)-nitro-2-(substitutedphenyl) benzo xazole, 2-(substitutedphenyl) oxazolo[4,5-b] pyridine derivatives	Inhibitor of TOP1 and TOP2	[31]
Lamellarin D	Inhibitor of TOP1	[32]
Hoechst 33342	Inhibitor of TOP1	[33]
3-(1H-indol-3-yl)-2,3,3a,4-tetrahydrothio chromeno[4,3-c] pyrazole derivatives	Inhibitor of TOP2	[34]
2,3-dihydropyrazino[1,2-a] indole-1,4-dione derivatives	Inhibitor of EGFR tyrosine kinase and mutant variant of serine/threonine kinase BRAF V600E	[35]
4-hydroxyquinazoline derivatives	Inhibitor of VEGFR2 tyrosine kinase	[36]
DW14383	Inhibitor of FGFR tyrosine kinase	[37]
Chimeric compounds containing piperazine and chalcone	Inhibitor of VEGFR tyrosine kinase	[38]
1,6-naphthyridone derivatives	Inhibitor of c-MET tyrosine kinase	[39]
N-sulfonylamidine derivatives	Inhibitor of c-MET tyrosine kinase	[40]
Di-2-pyridylketone 4,4-dimethyl-3-thiosemicarbazone (Dp44mT)	Inhibitor of AMPK protein kinase	[41]
Tigilanol tiglate	Activator of protein kinase C (PKC)	[42]
Epoxytigliane derivatives	Activators of protein kinase C (PKC)	[42]
Isoxazolo[4,5-e] [1,2,4] triazepine derivatives	Inhibitor of protein kinase C (PKC)	[43]
Pyrazolo[3,4-d]pyrimidine derivatives	Inhibitor of protein kinase D (PKD)	[44]
TAS-119	Inhibitor of AURKA protein kinase	[45]
Spirobibenzopyran derivatives	Inhibition of CDK4 protein kinase	[46]
Pyrazolo [3,4-d] pyrimidine derivatives (Si306 and Si113)	Inhibitor of CDK 1/2 protein kinases	[47]
7H-[1,2,4]triazolo[3,4- b] [1,3,4] thiadiazine derivatives	Inhibitor of GSK-3β protein kinase	[48]
Vinpocetine	*Activator of GSK-3β protein kinase*	[49]
Thiazolyl hydrazone derivatives	Inhibitor of ABL1 protein kinase	[50]
5-(3-chlorophenylamino) benzo[c][2,6] naphthyridine derivatives	Inhibitor Casein kinase 2 (CK2) 2	[51]
WZ4003	Inhibitor of AMPK-related kinase 5	[52]
N2817	Inhibitor of BET1vesicular membrane trafficking protein	[53]
Tetrazanbigen	Regulation of PPARγ expression	[54]
Calycosin	Regulation of apoptosis and miR-375 expression	[55]
3-bromopyruvate	Regulation of CTSB protease activity	[56]
Decursin	Regulation of HIF-1α transcription factor expression and degradation	[57]
Troglitazone	*Inhibitor of FOXM1 transcription factor activity*	[58]
Napabucasin	*Inhibitor of STAT3 transcription factor*	[59]
N-substituted sulfamoylbenzamide derivatives	Inhibitor of Il-6/STAT3 activity	[60]
Andrographolide	Regulation of ATF4 transcription factor activity	[61]
Quinoline derivatives	Inhibitor of phosphodiesterase (PDE5)	[62]
Osthole	Inhibitor of histone deacetylase (HDAC)	[63]
Empagliflozin	*Inhibitor of SGLT2 (SLC5A2) ion transporter*	[64]
Amb4269951	Inhibitor of choline transporter-like protein CTL1	[65]
Evodiamine	Inhibitor of HSP70 chaperone	[66]

Table continued

6-(7-nitro-2,1,3-benzoxadiazol-4-ylthio) hexanol (NBDHEX) derivatives	Inhibitor of GSTP1 glutathione transferase	[67]
BIBR1532	Regulation of TERT telomerase activity	[68]
Acetylshikonin	Inhibitor of DHFR dihydrofolate reductase	[69]
Docosahexaenoic acid derivatives	Inhibitor of bromodomain-containing protein 4 (BRD4)	[70]
Licochalcone A	Regulation of PD-L1 expression	[71]
2-amino-pyrrole-carboxamide derivatives	Inhibitor of tubulin polymerization	[72]
2,3-diaryl-2H-azirine derivatives	Inhibitor of tubulin polymerization	[73]
Indolizine derivatives	Potential inhibitor of tubulin polymerization	[74]
Rhein derivatives	Inhibitor of small GTPase Rac1	[75]
Dexamethasone	*Regulation of p65 activity*	[76]
Signaling cascades as targets		
Oleanolic acid and its semi-synthetic derivatives	PI3K/AKT/mTOR	[77]
Gypenoside derivatives	PI3K/AKT/mTOR	[78]
Cyanidin-3-O-glucoside derivatives	PI3K/AKT/mTOR	[79]
IPM712	PI3K/AKT	[80]
Thieno[3,2-d]pyrimidine	PI3K/mTOR	[81]
Artemisinin	Wnt/β-catenin	[82]
PRI-724	Wnt/β-catenin	[83]
Celastrol derivatives	HIF-1α	[84]
Decursin	HIF-1α	[85]
Ursolic acid	JAK2/STAT3/EGFR	[86]
Skullcapflavone I	JAK/STAT/MAPK	[87]
Gallothanin	JAK/STAT	[88]
Licochalcone A	MAPK	[89]
Chrysin-chromene-spiroxyindole derivatives	p53	[90]
Picropodophyllotoxin	JNK/p38	[91]
Luteolin	ERK/FOXO3a	[92]

Note: PPI — protein-protein interaction; * — approved medications are shown in italics.

STAT3, EGFR/GSK3B, ABL1/TERT, EGFR/MET, PRKCA/GSK3B, ABL1/STAT3, AURKA/GSK3B, PRKD1/EGFR, GSK3B/HSPA1A, GSK3B/NFKB1. It should be emphasized that the above mentioned interactions include proteins, which are involved in carcinogenesis regulation and are the targets for the approved anticancer drugs [99, 100].

Thus, bibliomertic analysis of papers, issued in 2020–2021, focused on the identification and development of the novel non-peptide anticancer drug prototypes revealed the following findings: i) a significant proportion (71%) of compounds belong to the chemical class of heterocycles, glycosides, quinones and terpenes; ii) indole, quinazoline, acridine and pyridine scaffolds were up to 35% from all used in organic synthesis of derivatives. Trend analysis of publication activity made it possible to define the scientific interest in the distinct groups of anticancer compounds and the progress in mapping their molecular targets. Among them, were proteins, associated with carcinogenesis, such as serine/threonine protein kinases, receptor tyrosine kinases, DNA topoisomerases and tubulins, which still remain the most studied anticancer drug targets. However, there are the increasing growth of the scientific interest in the design of inhibitors targeted to cancer-associated protein-protein complexes, transcription factors and metabolic enzymes, involved in the drug-resistant tumor phenotype.

CONCLUSIONS

Bibliometric approach with the using of Scopus, Reaxys, Pathway Studio and Cortellis databases together with VOS Viewer software enables prompt monitoring of the trends in the anticancer drug research and development (R&D) as well as defining the priorities in current scientific interest. At the same time, it can be said that there emerges a growing number a growing number of novel molecular modalities associated with carcinogenesis processes, which encorages the studies discovery of more efficient pharmacotherapeutic agents.

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