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## Review Article

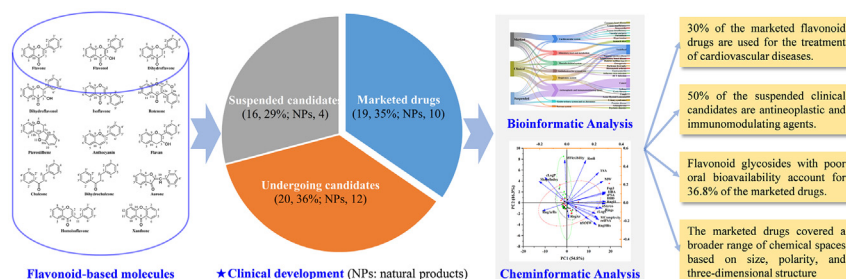
## Clinical development and informatics analysis of natural and semi-synthetic flavonoid drugs: A critical review

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## HIGHLIGHTS

- This is the most systematic review of flavonoid drugs and clinical candidates to date.
- 19 flavonoid drugs are approved for the market, while 36 candidates in clinical phases.
- 52.6% of the marketed flavonoid drugs and 44.4% of clinical candidates are natural sources.
- 30% of the marketed flavonoid drugs are used for the treatment of cardiovascular diseases.
- 50% of the suspended clinical candidates are antineoplastic and immunomodulating agents.
- Unexpectedly, flavonoid glycosides account for 36.8% of the marketed flavonoid drugs.

## GRAPHICAL ABSTRACT



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## ABSTRACT

**Background:** Flavonoids are one of the most important metabolites with vast structural diversity and a plethora of potential pharmacological applications, which have drawn considerable attention in the laboratory. Nevertheless, it remains uncertain how many candidates were progressed to clinical application. **Aim of Review:** We carried out a critical review of natural and semi-synthetic flavonoid drugs and candidates undergoing different clinical phases worldwide by applying an adequate search method and conducted a brief cheminformatic and bioinformatic analysis. It was expected that the obtained results might narrow the screening scope and reduce the cost of drug research and development.

**Key scientific Concepts of Review:** To our knowledge, this is the most systematic summarization of flavonoid-based drugs and clinical candidates to date. It was found that a total of 19 flavonoid-based drugs have been approved for the market, and of these, natural flavonoids accounted for 52.6%. Besides, a total of 36 flavonoid-based clinical candidates are undergoing or suspended in different phases, and of these, natural flavonoids account for 44.4%. Thus, natural flavonoids remain the best option for finding novel agents/active templates, and when investigated in conjunction with synthetic chemicals

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and biologicals, they offer the potential to discover novel structures that can lead to effective agents against a variety of human diseases. Additionally, flavonoid-based marketed drugs have been successful in cardiovascular treatment, and the related drugs account for more than 30% of marketed drugs. However, the use of flavonoids as antineoplastic and immunomodulating agents is not likely for approximately 50% of the candidates suspended in the clinical stage. Interestingly, the marketed drugs covered a broader range of chemical spaces based on size, polarity, and three-dimensional structure compared to the clinical candidates. In addition, flavonoid glycosides with poor oral bioavailability account for 36.8% of the marketed drugs, and thus, they could be thoroughly investigated.

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## Introduction

Flavonoids are a large group of natural metabolites that are especially abundant in plants. The first known use of the word ‘flavonoid’ was in 1947, and it generally referred to a large group of flavones and related analogs possessing only the C6-C3- fragment (2-phenyl chromogen ketone) [1–3]. Since 1952, flavonoids have been designated by the broader term ‘C6-C3-C6’ compounds, which have a basic 15-carbon flavone skeleton with two benzene rings (A and B) linked by a three-carbon pyran ring (C) [4]. Depending on the saturation level of the C-ring and the substitution position of the B-ring, the structure of the flavonoid compounds can be classified into 14 types of scaffolds, including flavone, flavanol, dihydroflavone, dihydroflavonol, isoflavone, rotenone, pterostilbene, anthocyanin, flavan, chalcone, dihydrochalcone, aurone, homoisoflavone, and xanthone (Fig. 1) [5–8]. The different types, numbers, positions and connection methods of substituents on these ‘C6-C3-C6’ carbon skeletons produce a wide variety of structural analogs with diverse biological activities. Their properties have been used as a primary source of medicines for early drug discovery.

According to available statistic data, more than ten thousand different flavonoids have been reported, and a considerable number of new structures are being reported every year [9]. Herein, we conducted a literature survey on the pharmaceutical research of flavonoids in the Web of Science (WoS) Core Collection Database, which was accessed on January 11, 2023, through the Shandong University of Traditional Chinese Medicine Library [10]. The search strategy was as follows: “Topic (flavonoid), refine by Document types (article & review article) and WoS categories (Pharmacology Pharmacy & Chemistry Medicinal), and no restrictions on other conditions”. A total of 16,607 results publications on the topic of flavonoids were obtained by using the WoS literature output function and CiteSpace deduplication function. Of these publications, 14,505 were original articles, accounting for approximately 87.3 % of all retrieved publications, while 2102 were review articles, accounting for 12.7 % of all retrieved publications. The number of publications gradually increased from 1986 to 2011 and then increased rapidly from 2012 to 2022 (with an average development rate of 5.4 %) (Fig. 2A). The top keywords with the strongest citation bursts showed that more attention has been given to antioxidants and oxidative stress (Fig. 2B).

Although there have been numerous excellent reviews that thoroughly summarize the potential therapeutic effects of flavonoid molecules on different aspects of human diseases in the past 37 years (from 1986 to 2022) [11–15], it remains unknown how many flavonoid analogs can be eventually developed as drug candidates and ultimately applied in clinics worldwide. As part of our ongoing investigations on natural flavonoids [16–25], we realized that clearly understanding the research progress of flavonoid-based drug development worldwide is imperative. Thus, our research group carried out a systematic data search through a joint professional big-data company “YAOZH” in China. Additionally, a

brief cheminformatic analysis was conducted using Data Warrior and principal component analysis (PCA) [26–28]. To our knowledge, this is the most systematic summary of flavonoid drugs and clinical candidates to date.

## Literature search strategy

### Search methods

To search the related flavonoid-based drug discovery and development thoroughly, we took the following two steps in conducting this study. First, a structured search of flavonoid-based compounds containing the 14 basic skeleton types (Fig. 1) was performed using the PubChem website (<https://pubchem.ncbi.nlm.nih.gov/>) through the “Draw Structure” method. After deduplication, more than 400,000 flavonoids were finally extracted. Second, key information, including the “CAS Number”, “international nonproprietary name (INN)”, and “China Approved Drug Names (CADN)” of these flavonoid-based molecules, was input into the Global Drug Database of YAOZH (<https://db.yaozh.com/>) to retrieve their drug development information. Notably, YAOZH is a leading open medical database in China that has a wealth of original databases and integrates data from domestic and foreign authoritative institutions to form a relatively comprehensive medical information resource, covering global drugs, drug registration, corporate reports, drug listings, and drug bids [29,30]. The obtained results were carefully rechecked in the [ClinicalTrials.gov](https://clinicaltrials.gov/), [AdisInsight](https://adisinsight.com/), and Google Scholar databases and are summarized in Table 1, which includes the compound name, CAS No., anatomical therapeutic chemical (ATC), therapeutic class (Indication), originator or developer, and highest phases.

### Analytical methods

A cheminformatic analysis was performed on the flavonoid-based drugs and clinical candidates, employing a previously established method with several modifications [31–33]. The structural and physicochemical parameters were calculated in the DataWarrior program (<https://openmolecules.org/>), an open-source data visualization and analysis program with embedded chemical and physical data [26,27], including the MW (Molweight), HBD (H-Donors), HBA (H-Acceptors), cLogP [P: conc(octanol)/conc(water)], cLogS [S: water solubility in mol/L, pH = 7.5, 25°C], RotB (Rotatable Bond Count), tPSA (Topological Polar Surface Area), Fsp3 (sp3-Atom Count/Total Carbon Atom Count), RngAr (Aromatic Rings Count), TSA (Total Surface Area, SAS Approximation, van der Waals radii, 1.4Å probe), relPSA (Relative Polar Surface Area, from polar and nonpolar SAS Approximation), nStereo (Stereo Center Count), nStMW (nStereo/MW), Rings (Small Rings Count), RngH (Small Ring Count with Hetero Atoms), RngHRs (RngH/Rings), RngArRs (Aromatic Ring Count/Rings), ShapeIndex (Shape Index), MFlexibility (Molecular Flexibility, low < 0.5 < high), and MComplexity

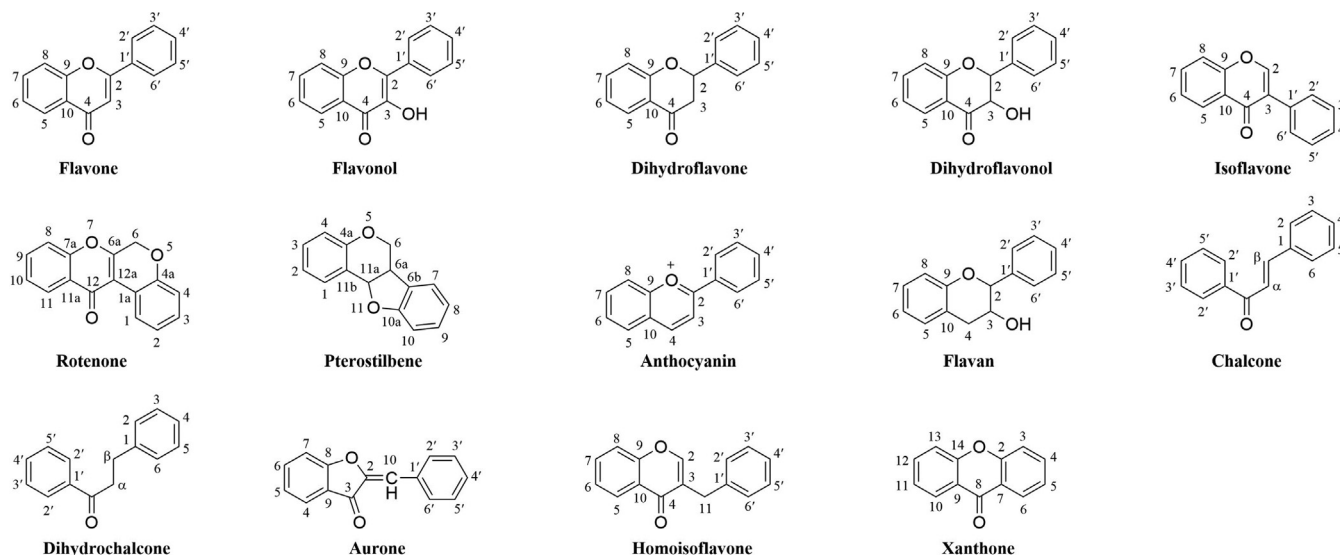


Fig. 1. The 14 basic skeleton types of flavonoid-based molecules.

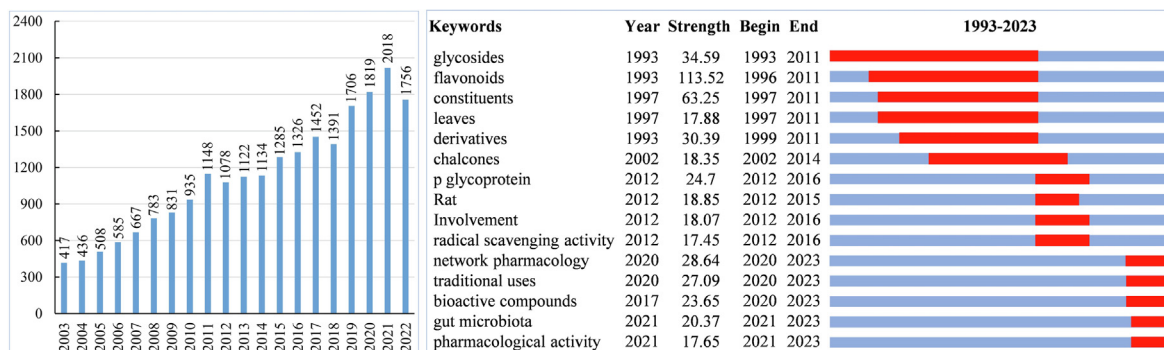


Fig. 2. A bibliometric data of flavonoids associated to pharmaceutical studies. (Left) Annual publications from 2003 to 2022; (Right) burst detection of the top 15 keywords from 1993 to 2022.

(Molecular Complexity, low < 0.5 < high)) (Supplementary Material, Table S1). Finally, principal component analysis (PCA) was used to visualize the distributions of the compound sets in chemical space, which is a statistical method that allows the complete 20-dimensional dataset to be visualized on two or three unitless, orthogonal axes, each representing a linear combination of the original 20 parameters [34]. The bioinformatic analysis of these flavonoid-based drugs and clinical candidates was performed using a previously published method [35]. Drug targets were collected from the DrugBank (<https://go.drugbank.com/>) and TTD (<https://db.idrblab.net/ttd/>) databases and imported into the DAVID 6.8 database (<https://david.ncicrf.gov/>) for Gene Ontology (GO) analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis ( $P < 0.05$ ). The related biological processes and signaling pathways involved in the key targets were analyzed, and the disease enrichment results were derived. The literature search was performed according to the aforementioned search criteria, and the search strategy is summarized in Fig. 3.

## Drug development history

According to our retrieval strategy, a total of 55 flavonoid-based drugs and candidates are summarized in this review (Table 1). Of these, 19 have been approved for medical prescription (1–19,

Fig. 4), 20 are undergoing clinical trials (20–39, Fig. 5), and 16 are not in progress in clinical research (40–55, Fig. 6).

## Flavonoid-based marketed drugs

Compound **1** (Eupatilin) is a major bioactive component of *Artemisia asiatica* Nakai ex Pamp. used in Korean traditional medicine that has been sold by Dong-A ST Co., Ltd. called Stillen<sup>®</sup> since 2002; it has been used for the treatment of gastric ulcer and gastritis [36]. Compound **2** (Diosmin<sup>®</sup>) was originally produced by Servier Pharmaceutical Co., Ltd. in France and is a new natural flavonoid derivative for the treatment of various hemorrhoids and chronic venous insufficiency [37]. Compound **3** (Recordil<sup>®</sup> 1956, efloxate, coronary vasodilator) and compound **10** (Remeflin<sup>®</sup> 1962, dimeflin, respiratory analeptic) are registered and commercialized as new original drugs in numerous countries by Recordati S.P.A [38,46]. In 1973, this corporation also developed a urinary anti-spasmodic compound, compound **11** (Genurin<sup>®</sup>/Urispas<sup>®</sup> and other brands, flavoxate). It was first synthesized in 1960 and developed in Italy before receiving FDA approval in the USA. It has been extensively used to treat urinary tract disorders induced by smooth muscle spasms, such as frequency of voiding, urgency to void, urine loss, suprapubic pain, pain during voiding and nocturnal voiding [47]. Primus Pharmaceuticals, Inc. of the United States previously developed an FDA-regulated medical flavonoid food

**Table 1**

Flavonoid-based marketed drugs (1–19) and candidates for clinical trials (or submitted to clinical trials) (20–55) undergoing or already excluded in different phases of pharmacological evaluation.

NO.	Compound name <sup>a</sup>	CAS No.	Anatomical Therapeutic Chemical (ATC)	Therapeutic Class (Indication)	Originator or Developer <sup>b</sup>	More advanced phase of research
1	Eupatilin [36]	22368–21-4	Alimentary tract and metabolism	Gastric ulcer; Gastritis	Dong-A ST Co. Ltd.; Korea	Marketed
2	Diosmin [37]	520–27-4	Cardiovascular system	Venous lymphatic insufficiency	Servier Pharmaceutical Co., Ltd.; France	Marketed
3	Eflorate [38]	119–41-5	Cardiovascular system	Coronary heart disease treatment, relieve angina pectoris	Recordati S.P.A., Italy	Marketed
4	Baicalin [39,40]	21967–41-9	Musculo-skeletal system	Osteoarthritis	Primus Pharmaceuticals, Inc.; United States	Marketed
			Antiinfectives for systemic use	Chronic hepatitis B	Jiangxi Puzhong Pharmaceutical Co., Ltd.; China	Marketed
5	Dosmalfate [41]	122312–55-4	Alimentary tract and metabolism	Duodenal ulcer; esophageal dysfunction	Faes Farma Co., Ltd.; Spain	Marketed
6	Scutellarin [42]	27740–01-8	Cardiovascular system	Angina pectoris; stroke; coronary heart disease	Yunnan Pharmaceutical Research Institute; China	Marketed
7	Disodium flavodate [43]	13358–62-8	Antineoplastic and immunomodulating agents	Reduce capillary fragility and permeability	Farmaceutici Formenti S.P.A., Italy	Marketed
8	Troxeutin [44]	7085–55-4	Cardiovascular system	Chronic venous insufficiency	Inpharma S.A.; France	Marketed
9	Icaritin [45]	118525–40-9	Antineoplastic and immunomodulating agents	Liver cancer	Shenogen Pharma Group Ltd.; China	Marketed
10	Dimeflin Hydrochloride [46]	2740–04-7	Respiratory system	Respiratory dysfunction	Recordati S.P.A., Italy	Marketed
11	Flavoxate [47]	15301–69-6	Genito-urinary system and sex hormones	Neuropathy; urinary incontinence; dysuria	Recordati S.P.A., Italy	Marketed
12	Hesperidin [48]	520–26-3	Cardiovascular system	Chronic venous insufficiency	Technological Unit of Nutrition and Health; Spain	Marketed
13	Silibinin [49,50]	22888–70-6	Alimentary tract and metabolism	Liver disorders; Poisoning	Rottapharm Madaus Co., Ltd; Italy	Marketed
14	umbralisib (TGR-1202) [51]	1532533–67-7	Antineoplastic and immunomodulating agents	Chronic lymphocytic leukaemia	Rhizen Pharmaceuticals S.A.; Switzerland	Marketed
15	Puerarin [52]	3681–99-0	Cardiovascular system	Myocardial infarction	Weifang Medical University, Shandong Provincial Academy of Medical Science, etc.; China	Marketed
16	Ipriflavone [53,54]	35212–22-7	Musculo-skeletal system	Osteoporosis	Takeda Pharmaceuticals Co., Ltd.; Japan	Marketed
17	Daidzein [55]	486–66-8	Cardiovascular system	Hypertension, coronary heart disease, cerebral thrombosis, vertigo	Liaoning Yihe Pharmaceutical Co. Ltd, China	Marketed
18	Catechin [56]	154–23-4	Musculo-skeletal system	Osteoarthritis	Primus Pharmaceuticals, Inc.; United States	Marketed
19	Sofalcone [57]	64506–49-6	Antiinfectives for systemic use	Stomach disease	Taisho Pharmaceutical Co., Ltd.; Japan	Marketed
20	Baicalein [58]	491–67-8	Antiinfectives for systemic use	Influenzas virus infections	CSPC Ouyi Pharmaceutical Co., Ltd.; China	Phase II
21	Wogonin [59]	632–85-9	Antineoplastic and immunomodulating agents	Liver cancer, breast cancer, leukemia	China Pharmaceutical University, China	Phase I
22	Alvocidib (Flavopiridol) [60,61]	146426–40-6	Antineoplastic and immunomodulating agents	Acute myeloid leukaemia; Germ cell and embryonal neoplasms	Sanofi-Aventis U.S. LLC; United States	Phase II
23	TP-1287 [62]	2044686–42-0	Antineoplastic and immunomodulating agents	Sarcoma; Solid tumors	Tolero Pharmaceuticals Inc.; United States	Phase I
24	Voruciclib (P1446A) [63]	1000023–04-0	Antineoplastic and immunomodulating agents	Acute myeloid leukaemia; B-cell lymphoma	Piramal Life Sciences Co., Ltd.; India	Phase I
25	Recoflavone [64]	203191–10-0	Alimentary tract and metabolism	Gastritis	Dong-A St Co., Ltd.; Korea	Phase III
26	Oroxylin A (CPU-118) [65]	480–11-5	Sensory organs	Dry Eye	Dong-A St Co., Ltd.; Korea	Phase II
			Antineoplastic and immunomodulating agents	Liver neoplasms, cellular lymphomas	China Pharmaceutical University; China	Phase I
27	Fisetin [66]	528–48-3	Musculo-skeletal system	Knee Osteoarthritis; Meniscus Repair	Austin V Stone; University of Kentucky; United States	Phase II
28	Quercetin [67]	117–39-5	Respiratory system	Chronic obstructive pulmonary disease	Internal Medicine, University of Michigan; United States	Phase II

Table 1 (continued)

NO.	Compound name <sup>a</sup>	CAS No.	Anatomical Therapeutic Chemical (ATC)	Therapeutic Class (Indication)	Originator or Developer <sup>b</sup>	More advanced phase of research
29	Isoquercitrin [68]	482–35-9	Cardiovascular system	Venous thromboembolism	Quercis Pharma AG; Switzerland	Phase III
30	Pinoцембрin [69]	480–39-7	Cardiovascular system	Ischemic stroke	CSPC ZhongQi Pharmaceutical Technology; China	Phase II
31	Naringenin [70,71]	93602–28-9	Antiinfectives for systemic use	Hepatitis C Virus; HCV Infection; Chronic HCV Hepatitis C	Massachusetts General Hospital; Harvard University; United States	Phase I
32	Naringin [72]	10236–47-2	Respiratory system	Cough	Sun Yat-Sen University; China	Phase I
33	Tenalisib [73]	1639417–53-0	Antineoplastic and immunomodulating agents	Breast cancer; Chronic lymphocytic leukaemia; Non-Hodgkin's lymphoma	Rhizen Pharmaceuticals S.A.; Switzerland	Phase II
34	Genistein [74]	446–72-0	Respiratory system	Pulmonary fibrosis	National Institutes of Health; United States	Phase III
35	Epicatechin [75]	490–46-0	Musculo-skeletal system	Friedreich's ataxia	Cardero Therapeutics, Inc.; United States.	Phase II
36	Epigallocatechin [76]	989–51-5	Antiinfectives for systemic use	Hepatitis C virus infection	Egyptian Liver Research Institute and Hospital (ELRIAH), Egypt	Phase III
37	ABBV-2222 (GLPG2222) [77,78]	1918143–53-9	Respiratory system	Cystic fibrosis	AbbVie, Inc.; United States	Phase II
38	Erteberel (LY500307) [79]	533884–09-2	Nervous system	Perimenopause-Related Depression	National Institute of Mental Health (NIMH); United States	Phase II
39	Elafibranor (GFT505) [80,81]	923978–27-2	Alimentary tract and metabolism	Primary biliary cirrhosis	GENFIT S.A.; France	Phase III
40	Mitoflaxone (FAA) [82]	87626–55-9	Antineoplastic and immunomodulating agents	Cancer	Lipha Pharmaceuticals; France	Not in progress <sup>c</sup>
41	Rivaciclib (P276-00) [83,84]	920113–02-6	Antineoplastic and immunomodulating agents	Mantle-cell lymphoma; Solid tumors	Piramal Enterprises Limited, India	Not in progress
42	PD 98,059 [85]	167869–21-8	Antineoplastic and immunomodulating agents	Cancer	Pfizer Inc.; United States	Not in progress
43	Aminoflovene (AFP-464) [86,87]	165179–35-1	Antineoplastic and immunomodulating agents	Breast cancer; Solid tumors	National Cancer Institute; United States	Not in progress
44	Flavodilol [88,89]	79619–31-1	Cardiovascular system	Hypertension	Pennwalt Corporation; United States	Not in progress
45	Vitexin [90]	3681–93-4	Antineoplastic and immunomodulating agents	Radioprotective effects	Vietnam Institute of Traditional Medicine, Vietnam	Not in progress
46	Upidosin (Rec 15/2739) [91]	152735–23-4	Genito-urinary system and sex hormones	Benign prostatic hyperplasia	Recordati S.P.A.; Italy	Not in progress
47	Terflavoxate [92]	86433–40-1 86433–39-8	Genito-urinary system and sex hormones	Urination disorders	Recordati S.P.A.; Italy	Not in progress
48	NPC-16377 [93]	139652–86-1	Nervous system	Neurological disorders; Psychotic disorders	Nova Pharmaceutical Corporation; United States	Not in progress
49	(±)-3'-Hydroxyfarrerol (IdB-1031) [94]	95272–99-4	Respiratory system	Respiratory tract disorders	Indena S.p.A.; Italy	Not in progress
50	Liquiritigenin [95]	578–86-9	Antineoplastic and immunomodulating agents	Menopausal hot flashes	Bionovo Inc.; United States	Not in progress
51	WS-7528 [96]	132147–69-4	Antineoplastic and immunomodulating agents	Cancer	Fujisawa Pharmaceutical Co. Ltd.; Japan	Not in progress
52	Silipid (IdB 1016) [97]	134499–06-2	Antineoplastic and immunomodulating agents	Ovarian cancer	Indena S.p.A.; Italy	Not in progress
53	Tectorigenin sodium sulfonate [98]	807636–25-5	Respiratory system	Acute respiratory infection and viral pneumonia	Sichuan Academy of Chinese Medicine Sciences; China	Not in progress
54	YM-26734 [99]	144337–18-8	Musculo-skeletal system	Rheumatoid arthritis	Yamanouchi Pharmaceutical Co. Ltd.; Japan	Not in progress
55	SU-740 [100]	134336–72-4	Alimentary tract and metabolism	Peptic ulcer	Taisho Pharmaceutical Co Ltd.; Japan	Not in progress

**Note:** a) The compounds can be referred to by their common name, trade name, or code name; b) The research team responsible for the initial discovery or development of the pharmaceutical compounds; c) Not in progress means there are no clinical trial updates after 01/01/2015.



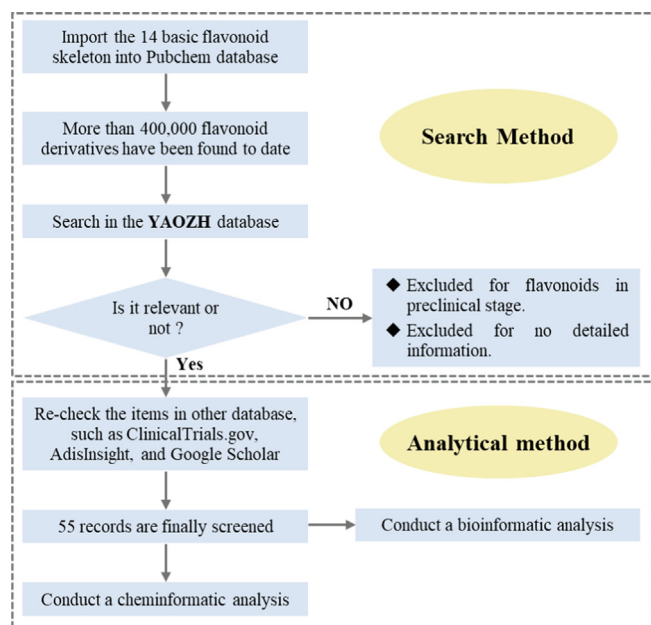


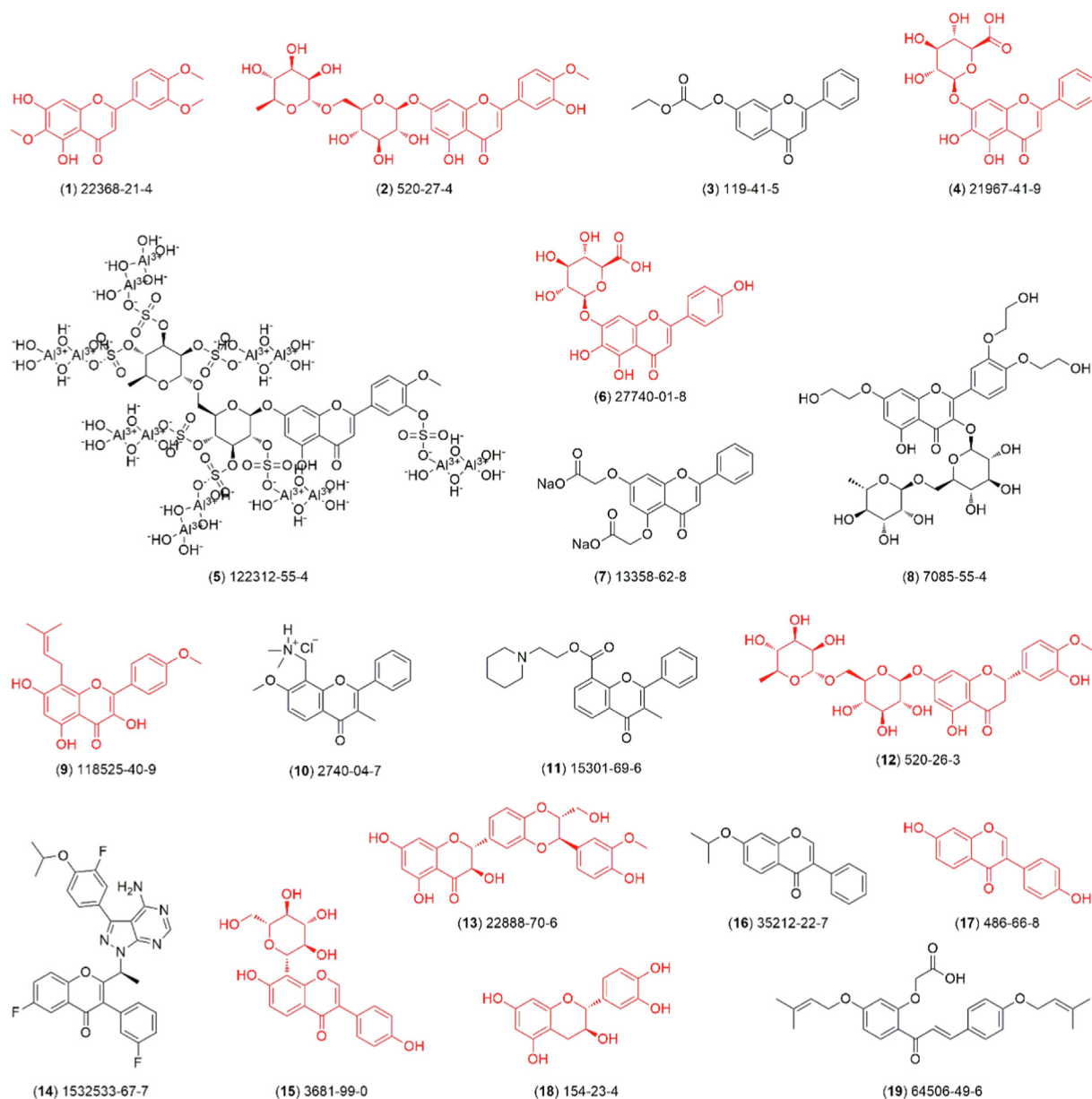
Fig. 3. Flavonoid search flow in databases showing inclusion or exclusion criteria for the data found.

product (Flavocoxid<sup>®</sup>) that is mainly composed of compounds **4** (baicalin) and **18** (catechin) and was used to treat knee osteoarthritis [39,56]. Jiangxi Puzhong Pharmaceutical Co., Ltd. of China also developed baicalin capsules for the treatment of chronic hepatitis B [40]. Compound **5** (Dosmaltate<sup>®</sup>) was developed and commercialized by Faes Farma Co., Ltd. for the treatment of duodenal ulcers and esophageal dysfunction in 2000 [41]. Compound **6** (scutellarin<sup>®</sup>), the major component of a Chinese traditional medicine, *Erigeron breviscapus* (Vant.) Hand.-Mazz., was developed for the treatment of angina pectoris, stroke, and coronary heart disease by Yunnan Pharmaceutical Research Institute of China in the 1980 s [42]. Compound **7** (disodium flavodate, Pericel<sup>®</sup>, LIRCA) is a synthetic hydrosoluble derivative of natural flavonoids that was developed by Farmaceutici Formenti S.P.A. for reducing capillary fragility and permeability [43]. Compound **8** (Trolox<sup>®</sup>) is a hemisynthetic flavonoid derivative of rutin that was developed by the Inpharma S.A. for the treatment of chronic venous insufficiency [44]. Compound **9** (Icaritin<sup>®</sup>, SNG-162) is a natural component isolated from *Epimedium brevicornu* Maxim, which was developed by Shenogen Pharma Group Ltd. of China. This drug targets the estrogen receptor subtype ER- $\alpha$ 36 to treat liver cancer and was approved for listing on January 10, 2022 [45]. Compound **12** (hesperidin<sup>®</sup>), a dihydroflavone glycoside rich in citrus fruits, was developed by the Technological Unit of Nutrition and Health of Spain as a new drug able to reduce several CVD (cardiovascular disease) risk factors. It was found to have glucose-lowering and anti-inflammatory effects in diabetic disease models, to have dyslipidemia-, atherosclerosis-, and obesity-preventing effects in CVDs and obese models, and to have antihypertensive and antioxidant effects in hypertensive disease models [48]. Compound **13** (Silibinin<sup>®</sup>) is a low-toxicity natural dihydroflavonol that was first isolated from *Silybum marianum*. It is considered the main bioactive component of silymarin, which was previously developed for the treatment of liver disorders and poisoning by Rottapharm Madaus Co., Ltd. of Italy [49,50]. Compound **14** (Umbralisib<sup>®</sup>, TGR-1202) was previously developed as an inhibitor of phosphatidylinositol 3-kinase delta (PI3K $\delta$ ) and casein kinase 1 epsilon (CK1 $\epsilon$ ) by TG Therapeutics for treating various hematological malignancies. Two years ago (2021), this compound received its

first approval in the United States for treating adults with relapsed or refractory marginal zone lymphoma (MZL) [51]. Compound **15** (Puerarin injection<sup>®</sup>) was jointly developed by Changwei Medical College (Weifang Medical University) from 1981 to 1985. It can significantly reduce the myocardial oxygen consumption index, effectively limit the myocardial infarction area, and reduce the myocardial infarction expansion rate, thereby significantly reducing the hospital mortality rate (6.6 % and 16.2 % in the administration and control groups, respectively) [52]. Compound **16** (Ipriflavone<sup>®</sup>) was first synthesized by Chinoin Pharmaceutical and Chemical Works Ltd. Hungary, and it could prevent the decrease in bone mass and mineral content in experimental animal models. In 1983, this compound was developed as a therapeutic drug for the treatment of osteoporosis in Japan. [53,54]. Compound **17** (daidzein) is the major bioactive ingredient of the nonsteroidal estrogens isolated from the traditional Chinese medicine *Puerariae Radix*, which was developed by Liaoning Yihe Pharmaceutical Co., Ltd., China, for treating hypertension, coronary heart disease, cerebral thrombosis, and vertigo [55]. Compound **19** (Sofalcone<sup>®</sup>) is characterized as a synthetic isopropyl flavonoid derived from the natural component “sophoradin”. Taisho Pharmaceutical Co., Ltd. of Japan previously developed it as an anti-gastric ulcer agent for increasing the amount of mucosal prostaglandin (PG) [57].

#### Flavonoid-based clinical candidates that are undergoing

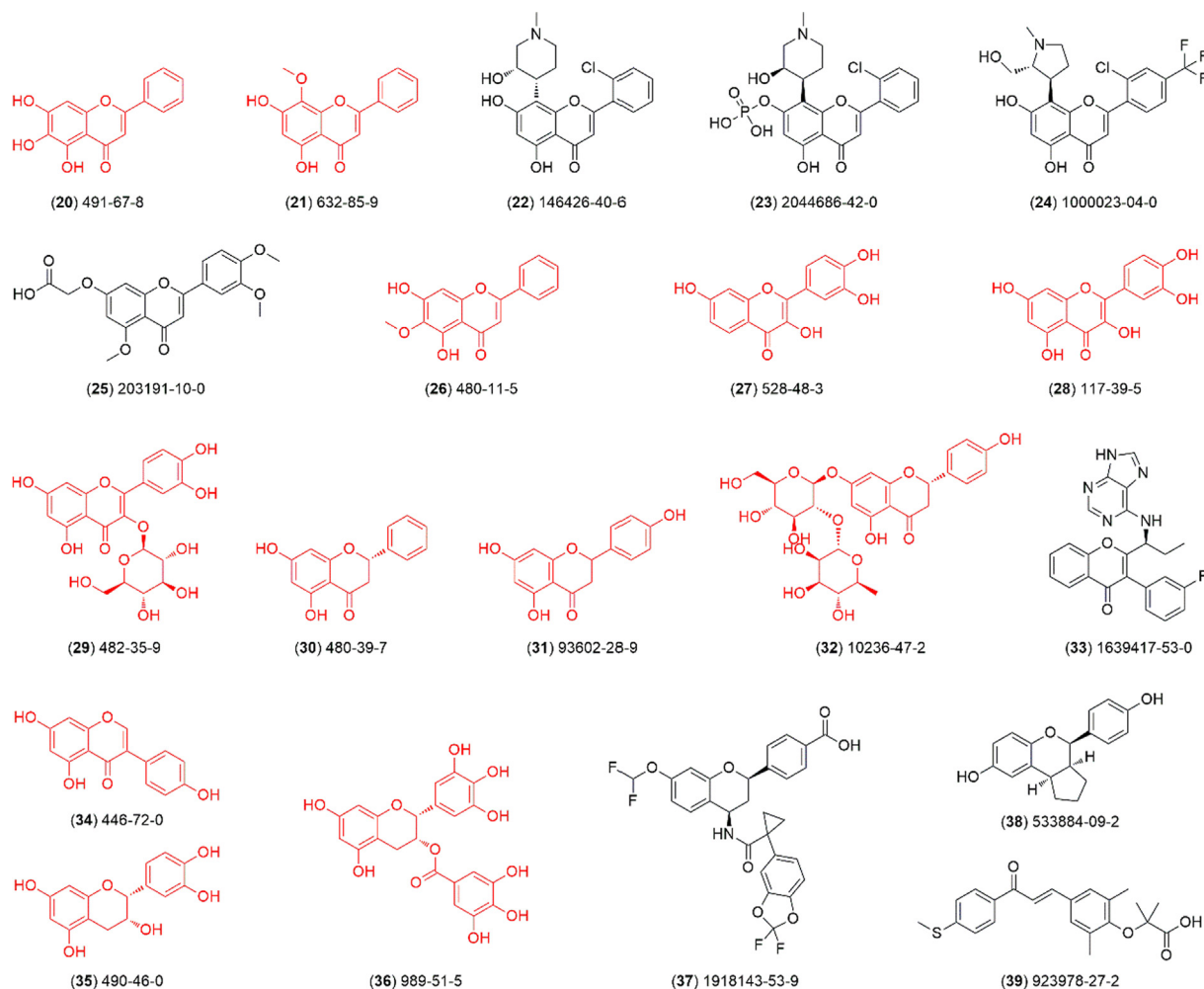
In addition to the above approved drugs, a total of 20 flavonoid-based drug candidates are undergoing different clinical phases. Compound **20** (Baicalein) is a natural flavone identified from *Scutellaria baicalensis* Georgi, a commonly used traditional Chinese medicine. It could improve the symptoms of COVID-19 through various mechanisms and has been advanced to Phase II clinical development by CSPC Ouyi Pharmaceutical Co., Ltd. of China [58]. Compound **21** (wogonin) is also a natural flavone from the roots of *S. baicalensis* Georgi. Researchers from China Pharmaceutical University found that it could selectively kill cancer with low toxicity to normal cells at concentrations that are lethal to tumor cells. Currently, this compound has been approved for Phase I/II clinical studies by the China Food and Drug Administration (CFDA) [59]. Compound **22** (alvocidib) was developed as an inhibitor of cyclin-dependent kinase 9 (CDK9) for treating acute myeloid leukemia and has currently progressed in a Phase II study (NCT02520011). It is also being evaluated in a Phase I clinical study evaluating the maximum tolerated dose, safety and clinical activity (NCT03298984, NCT03593915). In addition, it is being evaluated in a Phase I study in patients with relapsed or refractory acute myeloid leukemia in combination with venetoclax (NCT03441555) [60,61]. Compound **23** (TP-1287) was also developed as an investigational oral CDK9 inhibitor and has entered into a Phase I study in patients with advanced solid tumors (NCT03604783). When enzymatically cleaved, it can yield the parent drug alvocidib and showed better favorable oral bioavailability in preclinical models. [62]. Compound **24** (P1446A05) was previously synthesized as a selective CDK 4/6 inhibitor for killing multiple BRAF mutant and wild-type cell lines and is currently being evaluated in a Phase I study registered by Piramal Life Sciences Co., Ltd. of India [63]. Compound **25** (Recoavone, DA-6034) was first developed by Dong-A ST Co., Ltd. A Phase III clinical trial for this compound was previously completed (NCT01813812) in Korea for treating gastritis, and a Phase II trial (NCT01670357) for treating dry eye syndrome has also been completed. It could enhance the migration of gastric epithelial cells by activating mTOR and S6K1 downstream of PI3K [64]. Presently, there exists a dearth of information pertaining to the availability of DA-6034 within the South Korean market. However, the 2013 annual report of Dong-A Pharmaceutical reveals that Phase III clinical trials for DA-6034, specifically tar-



**Fig. 4.** Chemical structure of flavonoid drugs (1–19), with its CAS number, available for medical prescriptions. The ten compounds highlighted in red are of natural origin. The semi-synthetic routes for **3**, **7**, **8**, **10**, **11**, **14**, **16**, and **19** are detailed in Scheme S1 of Supplementary Material. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

getting gastritis indications, have been successfully concluded. Furthermore, the company's official website released a quarterly report in the fourth quarter of 2014, affirming the completion of Phase III trials for DA-6034 gastritis indications and projecting its imminent launch in 2015. Regrettably, the drug in question is conspicuously absent from the company's second quarter report of 2015. Compound **26** (Oroxylin) is also a natural flavone from *S. baicalensis* Georgi and has a reliable anticancer effect on human primary hepatocellular carcinoma cells with low toxicity. The research group of China Pharmaceutical University is currently developing this compound into a novel differentiation inducer agent for hepatoma [65]. Compound **27** (fisetin) suppressed osteoclastogenesis through the inhibition of RANKL-mediated ROS production by Nrf2-mediated upregulation of Phase II antioxidant enzymes. It was previously developed by Austin V Stone for treating knee osteoarthritis and has now entered the Phase II clinical stage [66]. Compound **28** (quercetin) is a natural flavonol and

has a potential therapeutic effect on chronic obstructive pulmonary disease (COPD). Researchers from the University of Michigan found that quercetin was safely tolerated up to 2000 mg/day as assessed by lung function, blood profile and COPD assessment test questionnaire [67]. Compound **29** (isoquercetin, Kinisoquin™) is also a natural active pharmaceutical constituent and was developed as an antithrombotic agent with a significantly lower risk of adverse events than existing preparations. Quercis Pharma AG of Switzerland previously initiated two Phase III clinical studies for the prevention of venous thromboembolism (VTE) in pancreatic cancer and glioblastoma patients [68]. Compound **30** (pinocembrin) was found to have a potent protective effect on the neurovascular unit, which could induce the relaxation of rat aortic rings through an endothelium-dependent and endothelium-independent pathway. Additionally, pinocembrin could improve rat cognitive impairments induced by chronic cerebral hypoperfusion. It is promising that pinocembrin could be developed for treat-

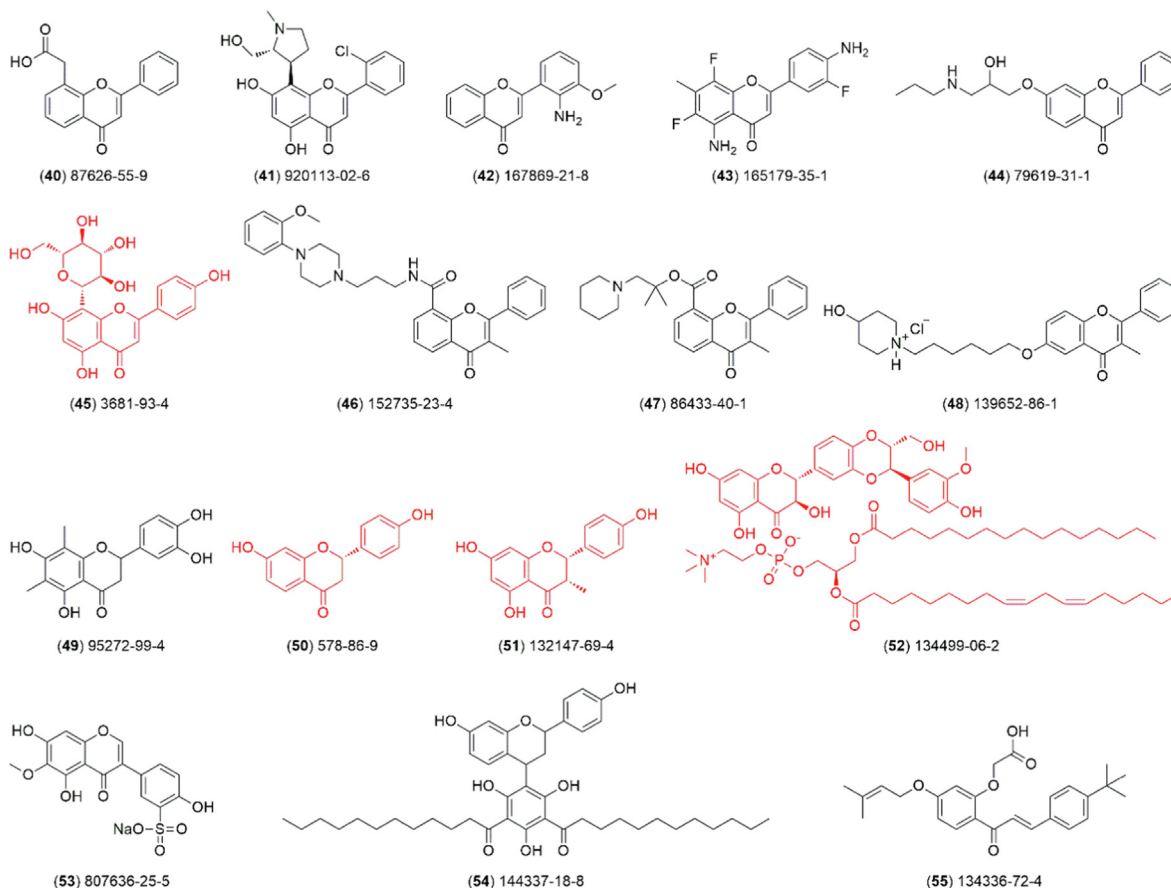


**Fig. 5.** Chemical structure of flavonoids (20–39) and its CAS number that are undergoing different phases of pharmacological studies. The 12 flavonoids highlighted in red are of natural origin. The semi-synthetic routes for 22–25, 33, and 37–39 are detailed in Scheme S2 of Supplementary Material. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

ing ischemic stroke and has been advanced to Phase I clinical development by CSPC ZhongQi Pharmaceutical Technology of China [69]. Researchers from the Massachusetts General Hospital Center previously found that nontoxic amounts of naringenin (compound 31) reduced hepatitis C virus secretion in infected cells by 80%. Injections of naringenin effectively reduced circulating VLDL (very low-density lipoprotein) levels in mouse plasma without toxicity [70,71]. Compound 32 (Naringin) exhibited anti-AHR (airway hyperresponsiveness) and antitussive effects on chronic cigarette smoke exposure-induced chronic bronchitis in guinea pigs and possesses novel therapeutic potential in the treatment of chronic bronchitis, which is currently being investigated in a Phase I clinical study by Sun Yat-Sen University of China [72]. Compound 33 (tenalisib, RP6530) could modulate the tumor microenvironment, resulting in the reprogramming of tumor-associated macrophages from a protumor M2 phenotype to an antitumor M1 phenotype and a marked reduction in angiogenesis in preclinical models. It was developed as a selective PI3K $\delta$ /g inhibitor with relapsed/refractory lymphoid malignancies in Phase I studies by Rhizen Pharmaceuticals S.A. of Switzerland [73]. Compound 34 (genistein) is a soy isoflavone that can induce the reversal of fibrosis and lung inflammation during pulmonary hypertension by mediating estrogen receptor  $\beta$ . It has progressed into a Phase III clinical study for treating pulmonary fibrosis by the National Institutes of Health (NIH) of the United States [74]. Compound 35 (epi-

catechin) could induce mitochondrial biogenesis and antioxidant metabolism in muscle fibers and neurons. A Phase II clinical study revealed that it was well tolerated over 24 weeks at up to 150 mg/d. Improvements in cardiac structure and function were observed in a subset of subjects with Friedreich's ataxia without statistically significant improvements in primary outcomes [75]. Researchers from the Egyptian Liver Research Institute and Hospital previously sponsored a Phase III open-label study for compound 36 (EGCG) and found that its incorporation interferes with viral entry mechanisms against HCV (hepatitic C virus) and in turn enhances efficacy and prevents relapse compared to the standard of care. Additionally, its anti-hemolytic and anti-fibrotic activities may improve the safety and tolerability of the therapy [76]. Compound 37 (ABV-2222) was first developed by AbbVie, Inc. of the United States and is currently being evaluated in Phase II clinical trials as a C1-corrector for treating cystic fibrosis. In a twofold Phase Ia clinical trial, a high dose of ABV-2222 markedly decreased sweat Cl concentrations in patients heterozygous for F508del [77,78]. Synthetic compound 38 (LY500307) was previously developed as a highly potent and selective ER $\beta$  agonist. It showed a 12-fold higher affinity for ER $\beta$  than ER $\alpha$  and exhibited 32-fold more functional potency. The National Institute of Mental Health of the United States previously sponsored a Phase I clinical trial (NCT03689543) for improving estradiol-withdrawal-induced mood symptoms in women with past perimenopausal depression





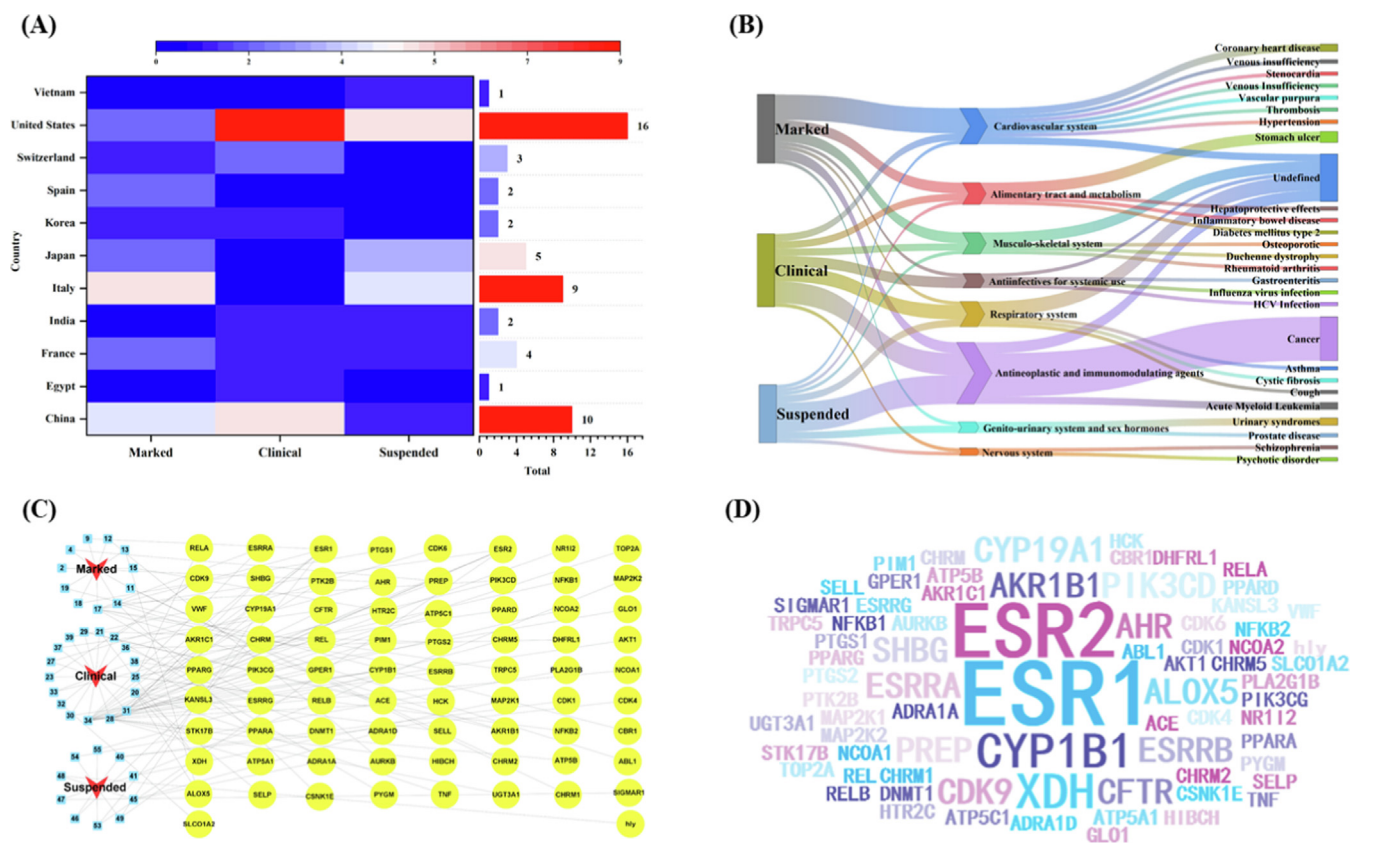
**Fig. 6.** Chemical structure of the flavonoids (40–55) that are clinical candidates suspended in different phases of pharmacological tests. The 4 compounds marked in red are of natural origin. The semi-synthetic routes for 40–44, 46–49, and 53–55 are detailed in Schemes S3 and S4 of Supplementary Material. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

[79]. Compound **39** (elafibanor) was synthesized as a novel agonist of peroxisome proliferator-activated receptor- $\alpha$  and - $\delta$ . GENFIT S.A. of France previously sponsored an international, randomized, double-blind, Phase II clinical trial (NCT03124108). They found that it was generally safe and well tolerated. It significantly reduced the levels of alkaline phosphatase (ALP), composite endpoints of bilirubin and ALP, and other markers of disease activity in patients with primary biliary cholangitis and an incomplete response to ursodeoxycholic acid[80,81].

#### Flavonoid-based clinical candidates that are suspended

In addition to the above marketed drugs and clinical candidates, 16 flavonoid-based candidates have also been suspended in clinical phases; that is, no recent clinical trials have been updated after 01/01/2015. For example, compound **40** (also named FAA, NSC 347512, LM 975, and flavone acetic acid) is a flavone synthesized by Lipha Pharmaceuticals of France. Its novel structure and unusual spectrum of activity in preclinical solid tumor models led to its introduction into clinical trials in the United States of America [82]. Compound **41** (raviciclib) is an inhibitor of several cyclin-dependent kinase (CDK) isoforms. Piramal Enterprises Limited of India previously sponsored a Phase II clinical study of P276-00 in patients with relapsed or refractory mantle cell lymphoma. Although relatively well tolerated, no desired pharmacological effects were observed for flavonoid **41** [83,84]. Compound **42** (PD 098059) was previously identified as a noncompetitive inhibitor of mitogen-activated protein kinase kinase-1 (MAPKK1) using a MAP kinase cascade assay comprising unphosphorylated MAPKK1

and unphosphorylated MAP kinase and monitoring phosphorylation of myelin basic protein [85]. Compound **43** (AFP-464) was a 5-aminoflavone derivative originally designed to inhibit the growth of the estrogen receptor-expressing MCF7 breast cancer cell line. The National Cancer Institute of the United States previously developed a Phase I clinical study of a once-weekly aminoflavone prodrug (AFP464) in solid tumor patients (NCT00348699) [86,87]. Compound **44** (flavodilol) is a new orally effective antihypertensive agent developed by Pennwalt Corporation of the United States. It extensively depleted catecholamines and serotonin in the heart tissue of normotensive and spontaneously hypertensive rats and has been previously advanced to Phase II clinical development [88,89]. Compound **45** (Vitexina) is derived from *Vigna radiata* (L.) Wilczek, which is widely used in Vietnam for detoxification. It was developed as a potent antioxidant radioprotective agent and introduced into a series of experimental studies conducted by the research team of the Vietnam Institute of Traditional Medicine [90]. Compound **46** (Rec 15/2739) showed excellent *in vivo* urethral selectivity in dogs, inhibiting prostatic urethral contractions at doses much lower than those required to lower basal blood pressure or induce orthostatic hypotension. For this, Recordati S.p.A. choose it for clinical development as a novel  $\alpha$ -1 adrenoceptor antagonist [91]. Additionally, Recordati S.p.A. previously investigated the antispasmodic effect of compound **47** (terflavoxate), a flavone derivative with spasmolytic properties in the urinary tract, by comparing it to the most common drugs utilized in the therapy of overactive detrusor [92]. Compound **48** (NPC16377) was first developed by Nova Pharmaceutical Corporation of the United States as a structurally novel and highly selective  $\sigma$  receptor ligand



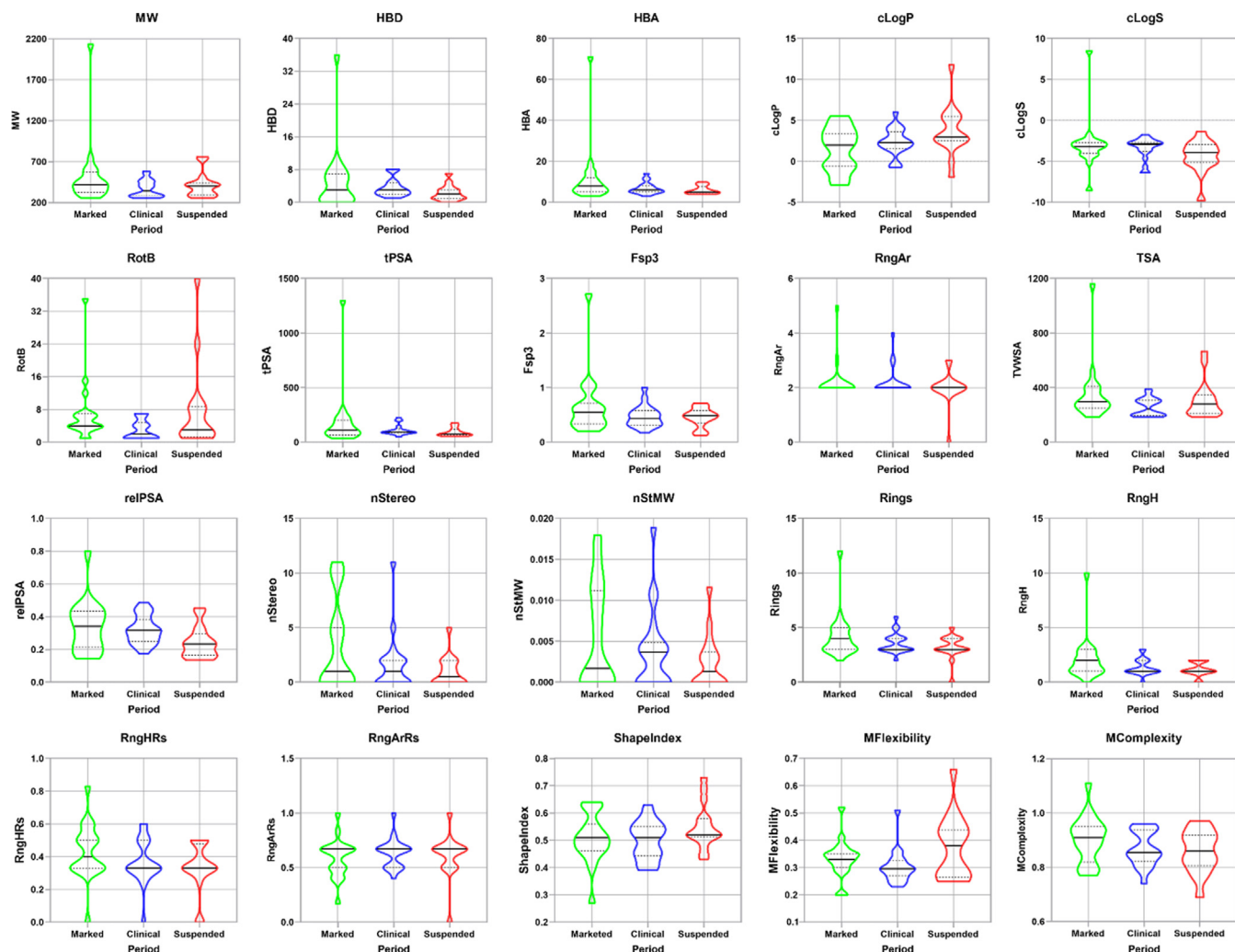
**Fig. 7.** General statistics of flavonoid-based drug discovery and development. (A) The distribution of originator or developer countries. (B) Sankey diagram of ATC classification. (C) Sankey diagram of drug-target-pathway for 55 flavonoid-based marketed drugs and clinical candidates. (D) Word cloud for 55 flavonoid-based marketed drugs and clinical candidates.

with low affinity for other neurotransmitter receptors. It was found that it exhibits a pharmacological profile similar to that previously ascribed to atypical antipsychotic drugs [93]. Compound **49** (IdB 1031) was considered as a good inhibitor of microsomal lipid peroxidation. Indena S.p.A. of Italy previously developed it as a clinical candidate for treating peroxidative damage associated with the induction of inflammatory responses and specifically with activation of a respiratory burst of leucocytes [94]. Compound **50** (liquiritigenin), a natural bioactive ingredient from *Glycyrrhizae uralensis* Fisch, could activate multiple ER (estrogen receptor) regulatory elements and native target genes of ER but not ER. ER selectivity was due to the selective recruitment of the coactivator steroid receptor coactivator-2 to target genes. Bionovo Inc. of the United States had previously tried to develop it as an antineoplastic and immunomodulating agent for treating menopausal hot flashes [95]. Compound **51** (WS-7528) was first extracted from cultured broth of *Streptomyces* sp. No. 7528. It could induce the growth of the estrogen-dependent cell line MCF-7 and showed weak anti-inflammatory activity on carrageenin rat paw edema. It has previously progressed to clinical development as an antineoplastic and immunomodulating agent by Fujisawa Pharmaceutical Co., Ltd. of Japan [96]. Compound **52** (IdB 1016) is a complex of silybin (the main active component of silymarin) and phosphatidylcholine in a molar ratio of 1:1 and was previously developed by Indena S.p. A. of Italy. This compound possesses greater oral bioavailability and therefore greater pharmacological activity than pure silybin or silymarin [97]. Compound **53** (tectorigenin sodium sulfonate) is a novel semisynthetic clinical candidate originating from the flavonoid active ingredients from *Belamcanda chinensis* (L) DC, which was developed for treating acute respiratory infections and viral pneumonia by the Sichuan Academy of Chinese Medicine Sciences

(CN 1594308A). It had previously entered the clinical phase in China (No. 2006L00092) [98]. Compound **54** (YM-26734) was developed as a potent and competitive inhibitor of extracellular phospholipase A<sub>2</sub> (PLA<sub>2</sub>), with selectivity for group II PLA<sub>2</sub>, by Yamanouchi Pharmaceutical Co. Ltd. of Japan. It was found that the inhibition of group II enzyme activity could suppress inflammatory responses to 12-O-tetradecanoylphorbol-13-acetate and carragenin [99]. A research group from Taisho Pharmaceutical Co Ltd. previously synthesized a new chalcone derivative (compound **55**, SU-740) with potent antiulcer activity. However, the aqueous solubility of SU-740 is very low, thus limiting the dosage form design and future clinical application [100].

#### Therapeutic class

It was found that the United States, China, and Italy are the first, second and third countries, respectively, with the greatest number of flavonoid-based marketed drugs and clinical candidates. Specifically, Italy developed the largest number of marked flavonoid drugs, while the United States has the largest number of clinical candidates with the majority of international cooperation partners. The candidates of China undergoing different clinical phases are also worthy of expectation (Fig. 7A). The flavonoid-based drugs and clinical candidates were further classified based on the Anatomical Therapeutic Chemical (ATC) system adopted by World Health Organization (WHO) (Fig. 7B). In the ATC system, substances are grouped according to the organ or physiological system on which they act, based on their chemical, therapeutic or pharmacological properties. It was found that all these drugs and candidates are distributed in eight categories, including alimentary tract and metabolism, cardiovascular system, anti-infectives for



**Fig. 8.** Results of the cheminformatic analysis on structural and physicochemical properties of flavonoid-based marketed drugs (1–4 and 6–19) and clinical candidates (20–51 and 53–55).

systemic use, antineoplastic and immunomodulating agents, respiratory system, genitourinary system and sex hormones, musculoskeletal system, anti-infectives for systemic use, and nervous system. Of these, the class of antineoplastic and immunomodulating agents account for the largest proportion of compounds (30.9 %), and this was followed by the cardiovascular system (18.2 %). In terms of the 19 marketed drugs alone, the cardiovascular system was the most common class (36.8 %), while antineoplastic and immunomodulating agents accounted for only 15.8 % of the compounds. Notably, antineoplastic and immunomodulating agents are the most common class (50 %) among the 16 suspended clinical candidates. That is, flavonoid-based drugs have been successful in cardiovascular treatment but are not ideal for the development of anticancer drugs.

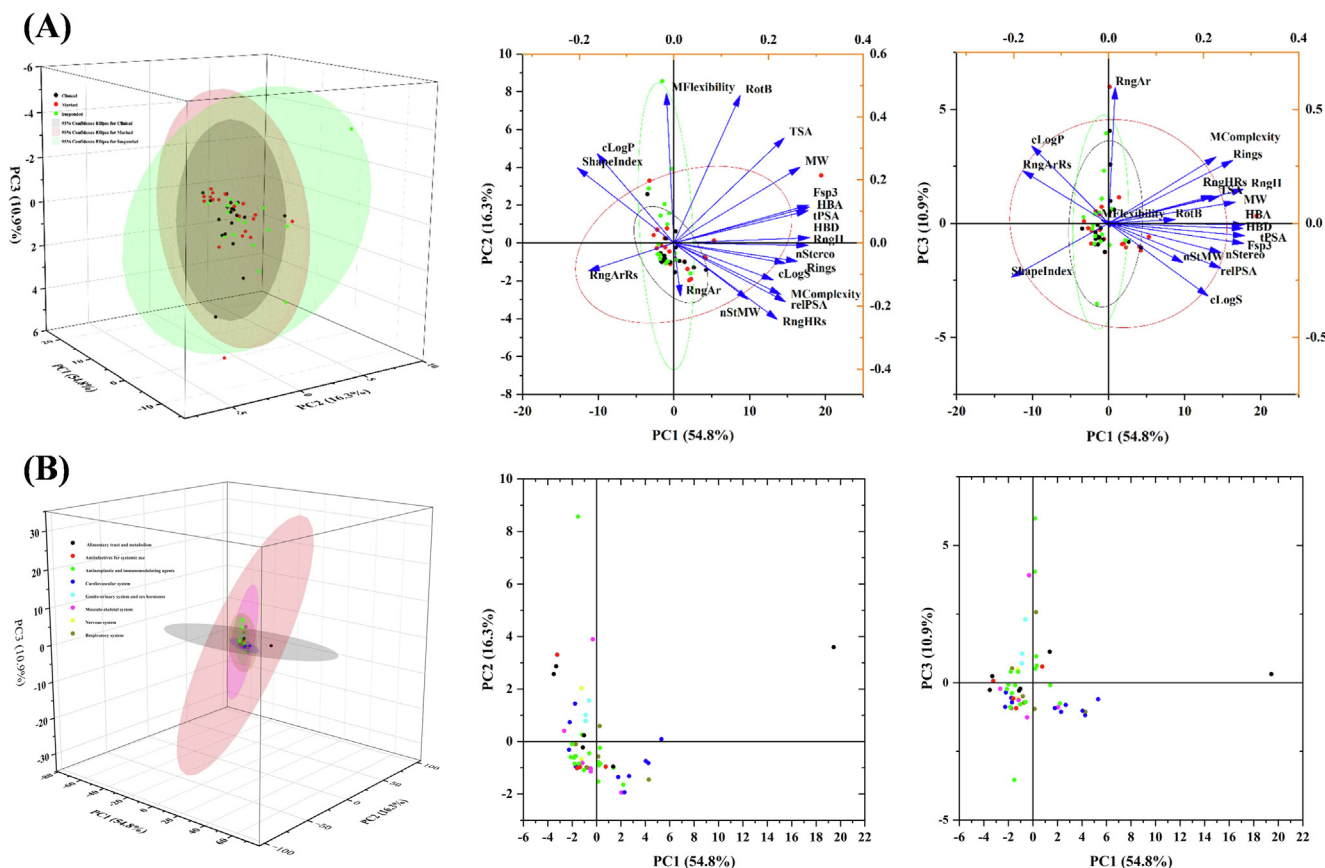
A brief bioinformatic analysis showed that 55 flavonoid-based marketed drugs and clinical molecules might act on 74 key targets collected from the DrugBank and TTD databases; of these targets, ESR1, ESR2, CYP1B1, and XDH were present at the highest frequency (Fig. 7C and 7D). Most flavonoid-based molecules correspond to a single target, but a few correspond to multiple targets, such as compounds **34** (genistein) and **28** (quercetin). Performing GO and KEGG functional enrichment analyses on the target genes can shed light on their involvement in various pathological conditions such as cancers, infectious diseases, endocrine and metabolic diseases, cardiovascular diseases, among

others (Supplementary Material, Figure S1). The bioinformatic analysis results were consistent with the results of the ATC system analyses.

### Structural features

Structurally, the 19 marketed flavonoid-based drugs could be classified as seven flavones (1–7), two flavonols (8 and 9), two 3-methylflavones (10 and 11), one dihydroflavone (12), one dihydroflavonol (13), four isoflavones (14–17), one flavan (18), and one chalcone (19). More specifically, compounds **4** and **6** are two glycosides with a glucuronic acid group, while **2**, **5**, **8**, and **12** possess an  $\alpha$ -L-rhamnopyranosyl-(1  $\rightarrow$  6)- $\beta$ -D-glucopyranose moiety. Compound **5** is a salt of aluminum sulfate with a large molecular weight of  $m/z$  2133.65, while compound **7** is a sodium carbonate with a small molecular weight of  $m/z$  414.03. Compound **5** could be synthesized from hesperidin by dehydrogenation, followed by sulfonation to the intermediate aluminum free dosimarate, which is then combined with basic aluminum chloride to form an aluminum salt complex of diosmin sulfate. The structures of compounds **10**, **11**, and **14** have at least one nitrogen heteroatom. Furthermore, compound **10** is a kind of quaternary ammonium salt, while compounds **11** and **14** were nonsalts with a nitrogen heterocycle unit.





**Fig. 9.** Results of the PCA and loading plots analysis on structural and physicochemical parameters of flavonoid-based marketed drugs (**1–4** and **6–19**) and clinical candidates (**20–51** and **53–55**).

The 20 ongoing clinical flavonoid-based candidates are composed of seven flavones (**20–26**), three flavonols (**27–29**), three dihydroflavones (**30–32**), two isoflavones (**33** and **34**), four flavanones (**35–38**), and one chalcone (**39**). Compared to the above drugs, these candidates contain more heteroatoms in their structures (**22–24**, **33**, **37**, and **39**). For instance, a piperidine ring was located at C-8 and a chlorine at the C-2 positions of both compounds **22** and **23**, and the C7-OH of compound **23** was substituted by a phosphate group. Compared to the structure of **22**, the substituent group at the C-8 position of **24** was a tetrahydrofuran ring, and the C4-H was replaced by a trifluoromethyl group. In the structure of compound **33**, a purine group was linked at the C-2 side chain to form an ammonia bond, and a fluorine was substituted at the C-3' position. There are four fluorine and nitrogen atoms in the structure of compound **37**, while a sulfur atom is located in the structure of compound **39**. In addition to the above structural features, compounds **29** and **32** could be further classified as two glycosides. The former is a glucopyranoside, while the latter possesses a moiety of  $\alpha$ -L-rhamnopyranosyl-(1  $\rightarrow$  6)- $\beta$ -D-glucopyranose.

The 16 suspended (not in progress) flavonoid-based candidates contain six flavones (**40–45**), three 3-methylflavones (**46–48**), two dihydroflavones (**49**, **50**), one 3-methyldihydroflavone (**51**), one dihydroflavonol (**52**), one isoflavone (**53**), one flavan (**54**), and one chalcone (**55**). The structures of such compounds (**41–44**, **46–48**, **52**, and **53**) have the most heteroatoms in comparison with those of flavonoid-based drugs and clinical candidates. For instance, a tetrahydrofuran ring and a chlorine atom were located at the C-8 and C-2' positions of compound **41**, respectively, while an amino group was substituted at the C-2' position of compound

**42**. The structure of compound **43** contains three fluorine atoms at the C-6, C-8, and C-3' positions and two amino groups located at the C-5 and C-4' positions. Compound **44** was produced by a dehydration reaction of 3-(propylamino)propane-1,2-diol and C7-OH. There is a piperazine ring linked at the C-8 position of compound **46** in the form of amide bonds, while a piperidine ring is located at the C-8 position of compound **47** in the form of an ester bond. There is also a piperidine ring located at the C-6 side chain in the structure of compound **48**, which exists in the form of quaternary ammonium salts. Compound **52** is a mixture of silibinin (**13**) and phosphatidylcholine. The most interesting thing about the structure of compound **53** is the C-3' position substituted by a sodium sulfonate group.

#### Cheminformatic analysis

The cheminformatic analysis was conducted using methods published by Professor Derek S. Tan with several changes on structural and physicochemical parameters [31–33]. The parameters were computed using the DataWarrior software and subsequently analyzed and visualized as a violin map using the Origin software (Fig. 8 and Supplementary Material, Table S1). The parameter distribution of clinical drugs is relatively concentrated, and marketed and suspended drugs have somewhat obvious discrete values. The marketed drugs had higher median values and scope compared to suspended drugs for multiple parameters, including H-acceptors (HBA), rotatable bonds (RotB), solubility (cLogS), total surface area (TSA), and ring counts (Rings, RngH, and RngHRs). In parameters normalized for molecular size, the marketed drugs also had higher sp<sup>3</sup> content (Fsp3) and relative polar surface area (relPSA). Con-



versely, the suspended drugs had higher hydrophobicity (cLogP) and fewer aromatic rings (RngAr) than the marketed drugs. Clinical drugs have higher solubility (cLogS) and stereochemical density (nStMW) than marketed and suspended drugs. Notably, the marketed drugs had the highest molecular complexity (MComplexity), while the suspended drugs had the highest molecular flexibility (MFlexibility).

We next used principal component analysis (PCA) to visualize the distributions of the compound sets in chemical space (Fig. 9A). PCA showed that the first three principal components retained 82 % of the variance in the total dataset, and > 90 % of the variance was included in the first five main components. The load diagram showed that the parameters related to molecular size (HBA, HBD, tPSA, Fsp3, and RngH) were highly correlated in the positive direction of the PC1 axis, and the HBA along the PC1 axis was the strongest. ShapeIndex significantly contributes to the negative variance of PC1. RotB and MFlexibility contribute more significantly to the conflict of the positive direction of PC2, while RngHRs have a greater contribution to negative suggestions. RngAr greatly influences the positive direction of PC3, while cLogS greatly influences the negative direction. The PCA results showed that the extension direction of the chemical space of the clinical drugs and approved drugs is highly similar, but the extension direction of the chemical space of the suspended drugs is markedly different from that of the clinical drugs and approved drugs. Compared with approved drugs, current clinical research drugs occupy less chemical space. The positive range of marketed drugs going deep into PC1 is more remarkable, consistent with the results of a more extensive range of molecular weights of marketed drugs. The positive upward extension range of the suspended drug PC2 is larger. The suspended drug 52 extends to the positive range of PC2 (to-8), and its molecular flexibility (RotB and MFlexibility) parameters are the largest.

The biological activity of a compound is influenced by its physical and chemical parameters. In this study, we conducted a PCA analysis (Fig. 9B) to explore the relationship between chemical parameters and pharmacological activity. The analysis revealed that the classes of antineoplastic and immunomodulating agents, as well as cardiovascular drugs, had the highest representation with 17 and 10 unique structures, respectively. The antineoplastic and immunomodulating agents were predominantly concentrated in the negative direction of the PC2 axis, while their distribution range was wide along the PC1 and PC3 axes. Cardiovascular drug compounds are distributed across all four quadrants of both the PC1 vs. PC2 axes. However, in the direction of PC3, there is a predominant concentration in the negative direction, indicating favorable hydrophilic properties. Anti-infectives for systemic use drugs exhibit the widest range of chemical space, which aligns with the diverse biological targets these drugs address. The alimentary tract and metabolism also exhibit a wide range along the PC1 axis due to the large size of compound 5. The genito-urinary system and sex hormones are positively distributed along the PC2 axis and demonstrate high CLogP values.

## Conclusion and perspectives

Flavonoids are important natural metabolites with vast structural diversity and a plethora of interesting pharmacological effects, which have drawn considerable attention in pharmaceutical research and development. The latest studies of natural and semi-synthetic flavonoid drugs used as therapeutic agents have not been systematically summarized. Therefore, we carried out a systematic summarization of flavonoid-based drugs and candidates undergoing different clinical phases worldwide by applying an adequate search method and conducted a brief cheminformatic

analysis. To our knowledge, this is the most systematic summarization of flavonoid-based drugs and clinical candidates to date. It was found that nineteen flavonoid-based drugs have been approved, and 36 candidates are undergoing or suspended in different clinical phases. Of these candidates, natural flavonoids account for 47.3 %. Thus, flavonoid-based drugs remain the best options for finding novel agents or active templates in drug development. In particular, flavonoid glycosides account for 36.8 % of the present marketed drugs. How is it possible for these glycoside drugs to be potentially developed into pharmaceuticals, even though they do not adhere to Lipinski's rule of five? It is conceivable that the impact of glycosylation on the bioactivity of flavonoids *in vitro* may diverge from that observed *in vivo*. Specifically, when administered orally, flavonoid glycosides exhibit comparable or even heightened bioactivity compared to their aglycone counterparts. Moreover, flavonoid glycosides exhibit elevated plasma concentrations and a prolonged mean residence time relative to aglycones [101]. Additionally, developing flavonoids for treating cardiovascular diseases seems to have a higher probability of success than developing them as antitumor drugs. The present review might narrow the screening scope and reduce the cost of drug research and development. Notably, we have tried our best to include all the information, but the retrieval method used in this article may also have its own limitations. If you find any inaccuracies in the relevant information, please do not hesitate to contact us.

## CRedit authorship contribution statement

**Kuo Xu:** Conceptualization, Writing – original draft, Funding acquisition. **Xia Ren:** Visualization, Writing – review & editing. **Jintao Wang:** Investigation, Resources. **Qin Zhang:** Investigation, Resources. **Xian-Jun Fu:** Conceptualization, Supervision, Funding acquisition. **Pei-Cheng Zhang:** Conceptualization, Supervision.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jare.2023.11.007>.

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