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Flavonoids and saponins: What have we got or missed?

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ABSTRACT

Background: Flavonoids and saponins are important bioactive compounds that have attracted wide research interests. This review aims to summarise the state of the art of the pharmacology, toxicology and clinical efficacy of these compounds.

Methods: Data were retrieved from PubMed, Cochrane Library, Web of Science, Proquest, CNKI, Chongqing VIP, Wanfang, NPASS and HIT 2.0 databases. Meta-analysis and systematic reviews were evaluated following the PRISMA guideline. Statistical analyses were conducted using SPSS23.0.

Results: Rising research trends on flavonoids and saponins were observed since the 1990s and the 2000s, respectively. Studies on pharmacological targets and activities of flavonoids and saponins represent an important

Abbreviations: AIF, apoptosis-inducing factor; ALT, alanine aminotransferase; AMD, age-related macular degeneration; AST, aspartate aminotransferase; ATM, ataxia-telangiectasia-mutated kinase; b.i.d., twice a day; CAP, child attention problems; CDK1, Cyclin-dependent kinase 1; CI, combination index; CK, compound K; CNKI, China National Knowledge Infrastructure; COX-2, cyclooxygenase-2; CPRS, Conner's Parent Rating Scale; CRC, colorectal cancer; CREB, cAMP-responsive element binding protein; CTRS, Conner's Teacher Rating Scale; CVI, chronic venous insufficiency; DPPH, 2,2-Diphenyl-1-(2,4,6-trinitrophenyl) hydrazyl; DR4, death receptor 4; DR5, death receptor 5; EMT, epithelial-mesenchymal transition; ErbB3, Erb-B2 receptor tyrosine kinase 3; FAK, focal adhesion kinase; FSFI, Female Sexual Function Index; GADD45A, growth arrest and DNA damage inducible alpha; GADD45B, growth arrest and DNA damage inducible beta; GATA3, tGATA binding protein 3; GRADE, Grading of Recommendations Assessment, Development and Evaluation; GTT1, gamma-glutamyltransferase 1; HbA1c, glycated haemoglobin A1c; HCC, hepatocellular carcinoma; HDL, high-density lipoprotein; hIMPDH, human inosine 5′-monophosphate dehydrogenase; HMPC, Committee on Herbal Medicinal Products; HO-1, heme oxygenase-1; HRG, histidine-rich glycoprotein; HUVECs, human umbilical vein endothelial cells; IGF-IR, insulin-like growth factor 1 receptor; IL-6, interleukine-6; iNOS, inducible nitric oxide synthase; IUPAC, International Union of Pure and Applied Chemistry; i.v., intravenous injection; IIEF, International Index of Erectile Dysfunction; LDL, low-density lipoprotein; MDA, malondialdehyde; MESSS, Modified Edinburgh-Scandinavian Stroke Scale; ME, mixture effect; MMP-2, Matrix Metalloproteinase-2; MMP-9, Matrix Metalloproteinase-9; MPFF, Micronized Purified Flavonoid Fraction; MSK, mitogen and stress activated protein kinase; mTOR, mammalian target of rapamycin; Nrf2, nuclear factor erythroid 2-related factor 2; NSAIDs, nonsteroidal anti-Inflammatory drugs; OS, oxidative stress; PD, pharmacodynamics; PICO, participants, intervention, comparison, and outcome; PK, pharmacokinetics; RCT, randomised controlled trial; PI3K, phosphatidylinositol-3-kinase; ROS, reactive oxygen species; PTEN, phosphatase and tensin homolog; TGF-β1, transforming growth factor beta 1; t.i.d., three times a day; TCM, traditional Chinese medicine; TNF-α, tumour necrosis factor-alpha; TRAIL, tumour necrosis factor-related apoptosis-inducing ligand; ΔΨm, mitochondrial membrane potential; WOMAC, Western Ontario and McMaster Universities.

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area of research advances over the past decade, and these important resources have been documented in open-access specialised databases and can be retrieved with ease. The rising research on flavonoids and saponins can be attributed, at least in part, to their links with some highly investigated fields of research, e.g., oxidative stress, inflammation and cancer; i.e., 6.88% and 3.03% of publications on oxidative stress cited by PubMed in 1990 - 2021 involved flavonoids and saponins, respectively, significantly higher than the percentage involving alkaloids (1.88%). The effects of flavonoids concern chronic venous insufficiency, cervical lesions, diabetes, rhinitis, dermatopathy, prostatitis, menopausal symptoms, angina pectoris, male pattern hair loss, lymphocytic leukaemia, gastrointestinal diseases and traumatic cerebral infarction, etc, while those of saponins may have impact on venous oedema in chronic deep vein incompetence, erectile dysfunction, acute impact injuries and systemic lupus erythematosus, etc. The volume of *in vitro* research appears way higher than *in vivo* and clinical studies, with only 10 meta-analyses and systematic reviews (involving 290 interventional and observational studies), and 36 clinical studies on flavonoids and saponins. Data are sorely needed on pharmacokinetics, *in vitro* pan-assay interferences, purity of tested compounds, interactions in complex herbal extracts, real impact of anti-oxidative strategies, and mid- and long-term toxicities. To fill these important gaps, further investigations are warranted. On the other hand, drug interactions may cause adverse effects but might also be useful for synergism, with the goals of enhancing effects or of detoxifying. Furthermore, the interactions between phytochemicals and the intestinal microbiota are worth investigating as the field may present a promising potential for novel drug development.

Introduction

As a result of co-evolutions, there are a tremendous number of bioactive compounds or secondary metabolites in various plants. These components are essential to a series of ecological functions, to protect against attacks by herbivores and microbes, serve as attractants for pollinators and seed-dispersing agents, and contribute to competition and invasiveness by suppressing the growth of neighbouring plant species. Humans exploit these compounds as flavouring agents, fragrances, and, especially, as sources of drugs (Osbourn and Lanzotti, 2009). These bioactive components include saccharides (polysaccharides), phenylpropanoids, phenols (polyphenols), flavonoids, alkaloids, saponins, tannins, resins, terpenoids, steroids, essential oils, organic acids, anthraquinones, etc. (Osbourn and Lanzotti, 2009).

Flavonoids are a huge family of over 5,000 polyphenolic compounds with a 15-carbon core structure. They often consist of two phenyl rings (A and B) and a heterocyclic ring (C) including an embedded oxygen, except for chalcones for which the ring C is cleaved. The main skeleton structures of flavonoids, flavone, flavonol, flavanone, flavanonol, anthocyanidin, flavandiol (flavanol), chalcone, catechin and isoflavone (Petrussa et al., 2013), are presented in Fig. 1. Flavonoids may be found in plants in O- and/or C-glycoside-bound and free aglycone forms, among which flavones and flavonols are the most common forms, notably present in daily diets all over the world.

The roles of flavonoids (from the Latin "*flavus*", meaning *"yellow"*) in plants include anti-oxidative stress, management of UV-light-induced damage, defense against phytopathogens, legume nodulation, male fertility, visual signals and control of auxin transport (Petrussa et al., 2013). For humans, they are also known as "Vitamin P" (Chen et al., 2020) (a controversial name, as they do not meet the definition of a vitamin), and they attract research attention for their effects on inflammation (Khan et al., 2020), neurological disorders (Khan et al., 2020), cancer (Dobrzynska et al., 2020), urolithiasis (Zeng et al., 2019), hypertension (Ellwood et al., 2018), venous insufficiency (Martinez-Zapata et al., 2020), etc.

Saponins are structurally divided into two groups, triterpene saponins and steroid saponins (Fig. 2). Triterpene saponin aglycones include the α-amyrane (e.g. ursolic acid) (Chen et al., 2012), β-amyrane (e.g. oleanolic acid) (Xia et al., 2012) and lupane (e.g. betulinic acid) skeletons (Yang et al., 2013), or the tetracyclic dammarane backbone (e.g. ginsenoside Rb1) (Kim et al., 2022) (Fig. 2A), linked with one to three carbohydrate chains containing up to six sugar or uronic acid molecules (Dewick, 2009). While steroid saponins consist of two groups, corresponding to spirostanol (e.g., dioscin) and furostanol (e.g., protodioscin) aglycones (Kang et al., 2017) (Fig. 2B).

Saponins function as defence compounds for plants and are pharmaceutically utilised by humans for their anti-thrombotic (Subramani and Sathiyarajeswaran, 2022), anti-inflammatory (Miranda et al., 2022), anti-cancer (Gupta et al., 2022), anti-diabetic (Lim and Park, 2022), and antihypertensive properties (Adeoye et al., 2022) and for treating reproductive disorders (Hamed et al., 2022).

Of note, although there is a large difference in structures between flavonoids and saponins, their reported applications impact oxidative stress- and inflammation-related major life-threatening diseases, such as

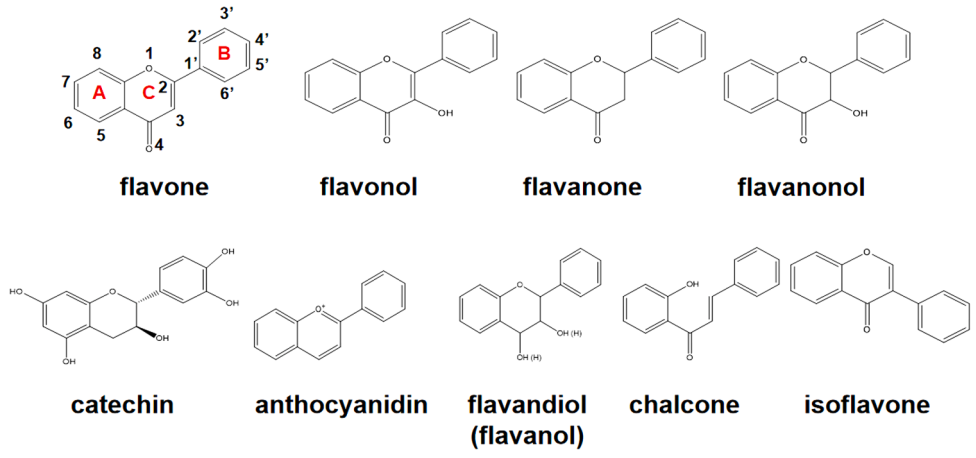

Fig. 1. The core structures of major flavonoids.

cardiovascular diseases, liver injury, neurological disorders and cancers. The purported positive impacts of flavonoids and saponins are so closely associated with such diseases that they attract huge attention of the research community worldwide. To better understand the significance of this trend of research, the present paper will critically review these compounds in the light of their popularity, nomenclature, purity, pharmacokinetics, pharmacodynamics and clinical use.

Material and methods

The trends of research were determined from the number of papers retrieved from PubMed, using the following searching strategies: "alkaloids"[Mesh]; "flavonoids"[Mesh]; "saponins"[Mesh]; "flavonoids/pharmacology"[Mesh]; "saponins/pharmacology"[Mesh]; "alkaloid and (oxidation OR oxidative)"; "flavonoid and (oxidation OR oxidative OR oxidative stress)"; "alkaloid and (cancer OR neoplasm OR tumour)"; "saponins and (cancer OR neoplasm OR tumour)"; "flavonoids and (hepatotoxicity OR liver injury)"; "flavonoids and (nephrotoxicity OR kidney injury)"; "saponins and (hepatotoxicity OR liver injury)"; "saponins and (nephrotoxicity OR kidney injury)". The reviewed papers were selected based on their relevance to the considered sections of the manuscript. Information on known targets was retrieved from the NPASS (Zeng et al., 2017) and HIT 2.0 databases (Yan et al., 2021) using the search terms "flav" and "sapo".

To compare the relationship between the phytochemicals and their pharmacological actions, the keywords “flavonoid”, “saponin”, “alkaloid”, “oxidative stress”, “inflammation” and “cancer” were retrieved in PubMed and Cochrane Library from 1990 to 2021. Concerning systematic review of clinical efficacy of flavonoids and saponins, the PRISMA criteria were followed (Moher et al., 2015; Page et al., 2021) and the two independent reviewers from Hubei Key Laboratory of Wudang Local Chinese Research (Prof. Xuanbin Wang and Mr. Hongliang Li) screened and double-checked the literature using the inclusion criteria as follows (Ding et al., 2019; Liu et al., 2021): (1) the literature involves the preventive and therapeutic effects of flavonoids and/or saponins; (2) the literature includes single Chinese medicinal herb extracts, and TCM formulas containing flavonoids and/or saponins; (3) the study involves a randomised and controlled design; and (4) the efficacy of flavonoids and/or saponins is investigated in clinical settings. The exclusion criteria were: (1) the literature is related to neither flavonoids nor saponins; (2) the concentration or proportion of flavonoids and/or saponins in the single herb or the Chinese formula are not quantified; (3) neither dosage nor concentration are available; (4) the study is not a randomized and controlled design; (5) the literature involves clinical studies without any ethical approval.

For statistical analyses, the data were analysed using SPSS23.0 (IBM SPSS Statistics, Armonk, USA). The analyses for different groups were conducted using One-way ANOVA (GraphPad Prism 5.0, San Diego, USA). $P < 0.05$ was regarded as statistically significant.

Results and discussion

A growing trend in research

The increasing popularity of a research can be grasped from the number of published papers. We selected alkaloids as a baseline comparator, the research in this field being relatively steady; indeed, despite a certain disaffection of the pharmaceutical industry (Daley and Cordell, 2021), alkaloids are still widely investigated to discover new drugs against tropical and neglected diseases, multi-resistant bacteria and cancer, or to decipher their multiple biological activities in, e.g. in cytotoxicity, pain or addiction. Fig. 3 shows a rising trend of research for flavonoids and saponins since the 1990s. Studies on direct pharmacological targets and agonistic or antagonistic activities of flavonoids represent an important area of research with significant progress in the past decade, especially the past 5 years. A PubMed search of *"Flavonoids/pharmacology"[Mesh] (direct*-target* OR affinity) (activat* or agonist or inhibit* or antagonist)* on 30th April 2022 led to 1,328 hits, among which 31.5% (418) and 47.4% (630) were published in the past 5 and 10 years, respectively. The same search on saponins led to 92 hits, with 33.7% (31) and 60.9% (56) of papers published over the last 5 and 10 years, respectively.

In the NPASS database (http://bidd.group/NPASS/), which documents 446,552 quantitative activity records (e.g. IC_{50}, EC_{50}, Ki, etc) of 222,092 natural product-target pairs, involving 25,041 species and 5,863 molecular targets (Zeng et al., 2017), the molecular targets of at least 378 flavonoids (search term "flav") and 108 saponins (search term "sapo") are documented (Suppl. Tables S1 and S2). In the HIT 2.0 database (HIT 2.0: http://hit2.badd-cao.net), which hosts 10,031 compound-target activity pairs with quality indicators, between 2,208 targets and 1,237 ingredients from more than 1,250 reputable herbs, the direct or indirect molecular targets of at least 100 herbal flavonoids and 24 saponins are documented (Suppl. Tables S3 and S4) (Yan et al., 2021).

The increasing scientific reports on flavonoids and saponins between 1990 and 2021 can be attributed, at least in part, to their proven or

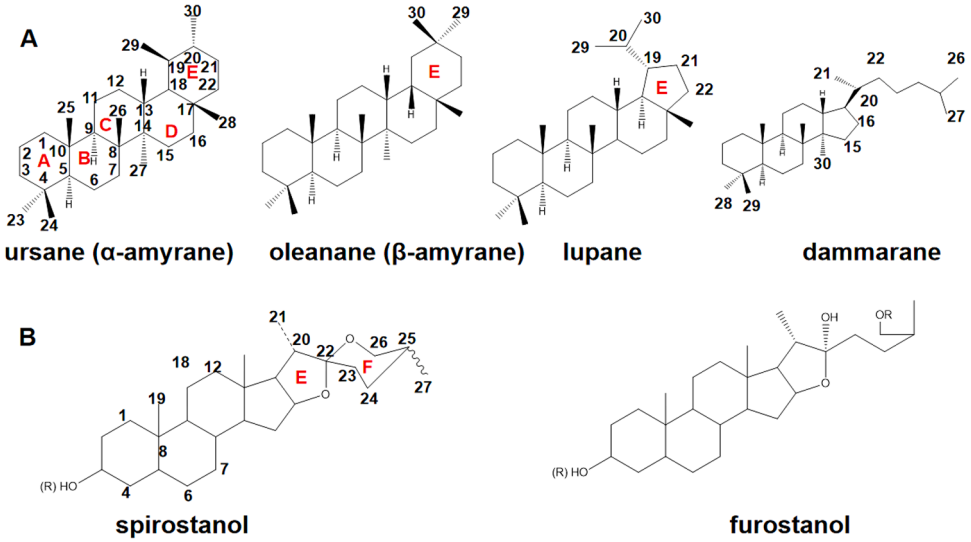

Fig. 2. The core structures of common saponins. The ring E of the typical triterpene structure is either a six-membered or five-membered ring, or cleaved.

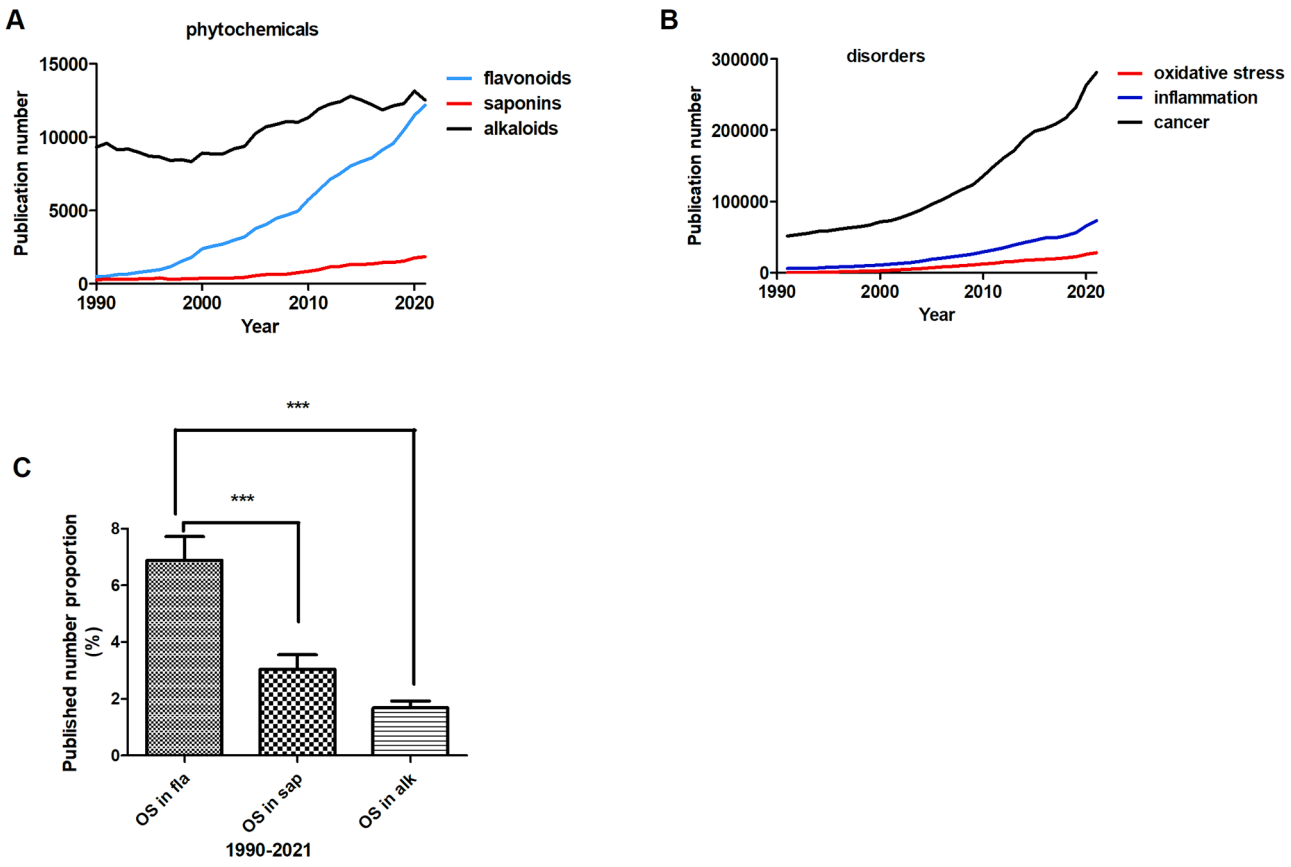

Fig. 3. Number of published papers on flavonoids and saponins correlated to oxidative stress, inflammation and cancer, with that of alkaloids as reference (data from PubMed, access date on April 29, 2022). A. Number of published papers on flavonoids and saponins; B. Number of published papers on oxidative stress, inflammation and cancer; C. The average proportions of published papers on oxidative stress (OS) for flavonoids (fla), saponins (sap) and alkaloids (alk) in PubMed from 1990 to 2021. ***: $P < 0.0001$ *vs*. OS in fla.

alleged links with a few but highly investigated fields of research, i.e. oxidative stress, inflammation and cancer (Fig. 3B). Linear regression analyses indicate that, the research trends of flavonoids and saponins fit the regression models of oxidative stress (R^2= 0.998 and 0.987), inflammation (R^2= 0.992 and 0.991) and cancer (R^2= 0.993 and 0.996), better than alkaloids (R^2<0.780) (Table 1).

The challenges of misleading assumptions inferred from nomenclature

When a new compound is isolated from a (medicinal) plant, it is customary to give it a name derived from this plant. For example, caffeine, rosmarinic acid or jujubosides were named after *Coffea sp, Rosmarinus spp.* and *Ziziphus jujuba* Mill, respectively. For flavonoids and saponins, even if the aglycone is already known, a subtle difference in the saccharide chain is enough to name a new compound, often under a name derived from the investigated plant name. For people coming afterwards, it may seem self-evident that compounds named as such are "the" important constituents in the considered plant and thus worthy of further pharmacological or standardisation studies. This assumption can be correct but can also be misleading; nonetheless, the frequent presence of some compounds and those highly cited in the literature often come to be considered as evidence of an *"important/interesting activity"*. In a vicious circle, this information can then be disseminated in numerous books, promotional literature and websites, becoming a mediatic truism that generates further research work that may or may not be warranted. Although a new chemical structure is named according to the nomenclature rules of International Union of Pure and Applied Chemistry (IUPAC), and attributed a Chemical Abstracts Service number (CAS NO), there is so far no rule regarding trivial names that are left to the discretion of discovering authors. Hence, we suggest that readers should pay attention to these possibly mystifying aspects.

The challenges of pharmacokinetics (PK).

In the wake of the concept of the 3Rs (replacement, reduction, and refinement) for animal studies (Lindsjö et al., 2016) and the ethical difficulties and costs of human studies, many groups resort to *in vitro* studies. Many *in vitro* models are very creative and some are quite

Table 1
Relationship between the number of published papers on phytochemicals and major disorders in PubMed. Trend analysis over 1990 to 2021.

	Oxidative stress		Inflammation		Cancer	
	Correlation (R^2)	Significance (*P*)	Correlation (R^2)	Significance(*P*)	Correlation (R^2)	Significance(*P*)
Flavonoids	0.998	0.000	0.992	0.000	0.993	0.000
Saponins	0.987	0.010	0.991	0.000	0.996	0.000
Alkaloids	0.744	0.001	0.738	0.001	0.779	0.755

Note: The access date was on April 29, 2022.

powerful, e.g., 3D cell culture, but most of these models lack a fundamental component of clinical pharmacology, namely, the PK aspects. This can be understood, as many natural flavonoids and saponins are not easy to obtain, thus limiting their PK and *in vivo* research. Flavonoid glycosides and saponins are characterised by *(i)* poor absorption properties with low membrane permeability; they seldom cross membranes "in their original form". It was long believed that flavonoids could not be absorbed in the intestine unless they are hydrolysed to the aglycones by gut biota. The later may then be partially absorbed or may undergo further biotransformation. Also, poor intestinal absorption of saponins (e.g., ginsenosides, licorice saponins, dioscorea saponins, astragalosides, or saikosaponins) is mainly due to their unfavourable physicochemical traits, such as large molecular mass (> 500 Da), high hydrogen-bonding capacity (>12), and high molecular flexibility (> 10), which underlie poor membrane permeability (Walle, 2004; Yu et al., 2012); *(ii)* a difficult-to-predict metabolism in the digestive gut, probably resulting in saccharide chain hydrolysis and structure modifications, especially for flavonoids (Cassidy and Minihane, 2017) but also for saponins (He et al., 2019b); the impact of the intestinal microbiota is important (Murota et al., 2018; Pferschy-Wenzig et al., 2017) and may yield metabolites with activities quite different from those of the parent compounds; *(iii)* a likely direct impact on the digestive tract cells and intestinal flora, that may modulate a series of signalling addressed to different body systems (Grundy, 2006; Sekirov et al., 2010); *(iv)* an eventual impact on the gut flora (selective growth promotion of specific bacteria, induction/repression of bacterial metabolism); and *(v)* a difficult-to-predict liver metabolism of absorbed molecules, complicated by an individual variety dependent on a number of factors, including age, sex, and genetic polymorphism. The plant source and food matrix certainly modulate these impacts too. Therefore, for both flavonoids and saponins, the transposition of *in vitro* data to an *in vivo* or clinical situation is unlikely straightforward and many unknowns challenge the conclusions sometimes hastily drawn, mainly from *in vitro* evidence, for highly reported supposedly active compounds (Li et al., 2022).

The challenges of pharmacodynamics (PD).

The challenges of pan-assay interferences and chemical purity

Most of the research on natural products relies on bioassay-guided purifications, aiming at pinpointing and isolating the molecules that show the strongest activity in a given biological assay. However, some pan-assay interfering compounds (so-called *"pains"*) typically show up as reproducible hits in many different assays but can rarely be optimised into specific drugs; interferences can arise from fluorescence or bioluminescence quenching, optical opacity (absorption, light scattering) in UV-Vis, precipitation of an analyte or aggregation of proteins, metal chelation (impact on enzymes, on cell viability), chemical reactivity and redox effects (e.g. redox cycling), or surfactant properties (membrane perturbation/disruption in cell-based assays) (Baell, 2016; Bisson et al., 2016). Bisson et al (2016) listed 39 natural compounds heavily over-represented for occurrence and (distinct) activity in the Napralert database; from these, 11 are flavonoids (quercetin, genistein, rutin, kaempferol, apigenin, luteolin, isoquercitrin, myricetin, catechin, epicatechin, epigallocatechin gallate) and 3 are saponins (glycyrrhizin, ginsenosides Rb1 and Rg1) (Bisson et al., 2016). According to their likelihood in bioassay interfering, such "*pain*" compounds are effectively detected in many activity-based schemes, leading to significant efforts in purification and/or dereplication. These "*pains*" are now being flagged in many high-throughput screening systems (Capuzzi et al., 2017); on the other hand, it is documented that the indiscriminate application of "*pains*" alerts could discard viable drug candidates (Chai and Mátyus, 2016; Senger et al., 2016) because such alerts have actually been found in approved drugs (Capuzzi et al., 2017).

In fact, the repeated identification of the same types of molecules as promising hits in different bioassays may either compromise the reliability of the bioassay-based approach (Baell, 2016), *"polluting"* the literature in a difficult-to-estimate manner, or yield important data on overarching targets that impact a huge series of pathways.

A challenge also resides in the purification of active fractions; the purity of tested compounds is rarely described, and it is possible that very active minor impurities accompanying a supposedly purified compound could be the real active compounds or interfere with the guiding bioassay (Bisson et al., 2016).

The probably over-rated importance of antioxidants

Oxidative stress (OS) is important in many pathologies. Inflammation (Mahmoud et al., 2021) and cancer (Yang et al., 2019) were reported to be associated with OS. This may be the reason that the numbers of papers on flavonoids and saponins are closely associated with oxidative stress, inflammation and cancer (Table 1 and Fig. 3). Furthermore, the proportions of papers dealing with OS was considerably higher for flavonoids (13.0%), compared to saponins (8.1%) and alkaloids (4.3%) in 2021. From 1990 to 2021, the average proportion of OS papers for flavonoids, saponins and alkaloids were 6.9%, 3.0% and 1.9%, respectively ($P < 0.0001$). This indicates that the research interests of anti-oxidative effects for flavonoids are more popular than that for saponins and alkaloids (Fig. 3C). However, it is now admitted that antioxidative therapies are not as effective/important as expected in the 1990s. For example, quercitrin, a common flavonoid antioxidant, has been reported possibly useful in various disorders associated with oxidative damage, i.e., inflammation or infections, and for immunomodulatory, analgesia, wound healing, and vasodilatory properties. However, clinical studies of quercitrin are insufficient at present to conclude on its real interest (Chen et al., 2022), indicating that further high-quality studies are still needed before recommending a clinical use for such natural products.

Multiple targets and complex mechanisms of anticancer and anti-inflammatory activities, etc.

The anticancer mechanisms of flavonoids and saponins can be categorised according to the cancer hallmarks recently outlined by Hanahan (Pan et al., 2016). First, a number of flavonoids have been reported to repress proliferative signalling in cancer cells. For example, naringin and naringenin (Memariani et al., 2021), apigenin, baicalein and fisetin (Hosseinzadeh et al., 2020), myricetin (Yang et al., 2017) and kaempferol (Homhual et al., 2006) suppress cancer cell proliferation by inhibiting phosphatidylinositol-3-kinase (PI3K)/Akt and mTOR signalling pathways. Second, some flavonoids are known to overwhelm the evading growth suppressors of cancer. For example, kaempferol (Li et al., 2019a), oleanolic acid (Hosseinzadeh et al., 2020), naringin and naringenin (Memariani et al., 2021) inhibit transforming growth factor beta (TGF-β) to counter malignancy; oleanolic acid down-regulates miR-122/cyclin G/MEF2D, while baicalein up-regulates p53 and blocks ezrin to arrest cell cycles (Hosseinzadeh et al., 2020). Flavonoids have also been reported to induce apoptosis, autophagy and other types of cell death in cancer cells. For example, myricetin decreases mitochondrial membrane potential ($\Delta\Psi m$) in ovarian cancer cells (Yang et al., 2017); morin and chalcones (Hosseinzadeh et al., 2020), baicalein (Xie et al., 2013), naringin (Hosseinzadeh et al., 2020) and kaempferol (Lee et al., 2016) activate caspase cascade to induce apoptosis in cancers. Some flavonoids may also target cancer angiogenesis. For instance, kaempferol is known to increase reactive oxygen species (ROS), Caspase-8, Caspase-9, DR4/5, and ATM/p53, and to inhibit the proliferation of human umbilical vein endothelial cell (HUVECs) (Lee et al., 2016); while baicalein inhibits vascular endothelial growth factor (VEGF) and fibroblast growth factor receptor-2 (FGFR-2). Some flavonoids, e.g. baicalein (Xie et al., 2013), kaempferol (Li et al., 2019a) and morin (Hosseinzadeh et al., 2020) are also known to block MMP-2 and MMP-9, which are known to play important roles in invasion and metastasis of cancer. Other phytochemicals that may inhibit cancer invasion and metastasis include genistein, which down-regulates focal adhesion kinase (FAK) (Hosseinzadeh et al., 2020), and luteolin, which

reverses epithelial mesenchymal transition (EMT) (Imran et al., 2019). Flavonoids, e.g. naringin and naringenin, may also affect the crosstalk between inflammation and cancer by repressing related transcription factors and cytokines (Memariani et al., 2021).

In inflammation, both pro-inflammatory and anti-inflammatory mediators are involved and can become potential therapeutic targets (Miranda et al., 2022). Some saponins (ternstroenol C, D, E; sanchakasaponin G, vuchasaponin A, and 3-O-[α-D-Rhamnopyranosyl-(1→2)]-[β-D-galactopyranosyl-(1→3)]-[β-Dglucopyranosyl-(1→2)]-[β-Dglucuronopyranosyl]-22-*O*-[2E,4E]-octa-2,4-dienoyl-barrigene) inhibit pro-inflammatory factors in lipopolysaccharides (LPS) and IFN-γ-activated RAWW 264.7 macrophages with IC_{50} value less than 5 μM (Singh et al., 2020); other saponins inhibit NO production with IC_{50} less than 10 μM (Cyclocarioside X, Y and Z_2) (Liu et al., 2020), and NF-κB (IC_{50} value 1.4 μM) and COX-2 (IC_{50} value 0.37 μM) (bruguierins A) (Homhual et al., 2006), TNF-α (IC_{50} value 52.4 μM) and IL-6 (IC_{50} value 32.4 μM) (terpenes from *Schefflera rubriflora* C. J. Tseng & G. Hoo) (Li et al., 2019a); whilst the anti-inflammatory and neuroprotective mechanisms of the flavonoid hesperetin are associated with down-regulation of pro-inflammatory factors NF-κB and MAPK (Khan et al., 2020). Pectolinarigenin, a flavonoid from *Aegiphila integrifolia* (Jacq.) B.D.Jacks, exerts anti-inflammatory and neuroprotective effects via enhancing the anti-inflammatory cytokine IL-10 at the concentrations of 1 and 5 μM (Heimfarth et al., 2021). The flavone wogonin promotes hematoma clearance and improves neurological recovery through inducing Axl, MerTK, CD36, and LAMP2, and reducing TNF-α, IL-1β, and iNOS (Zhuang et al., 2021).

Besides, *Rhodiola spp*. extracts (including the flavonol herbacetin) alleviate cardiac hypertrophy through down-regulating serum/glucocorticoid regulated kinase 1 (SGK1) (Zhang et al., 2022b). Flavonoids from *Canna x generalis* L.H. Bailey treat colitis via inhibiting TLR4/NF-κB and NLRP3 (Mahmoud et al., 2021). Total flavonoids from *Glycyrrhiza uralensis* Fisch. protect liver from injury via increasing superoxide dismutase (SOD) and glutathione (GSH) (Gou et al., 2021) whilst kaempferol alleviates neurotoxicity via down-regulating GSK3β-Nrf2 (Hussein et al., 2018). Saponins from various plants have been investigated for antifungal/antiyeast activities (*Maesa lanceolata* Forssk., *Panax notoginseng* (Burk.) F.H. Chen, *Colubrina retusa* (Pittier) R. S.Cowan, Yucca schidigera Roezl. ex Ortgies, *Hedera colchica* (K.Koch) K. Koch, etc.), for antibacterial/antimicrobial activity (*Hedyotis nudicaulis* Wight & Arn., *Colubrina retusa* (Pittier) R.S.Cowan, *Capsicum annuum* L. var. *acuminatum* Fingerh., etc.), for antiparasitic activity (*Glinus oppositifolius* Aug.DC., *Hedera helix* L.), for aphrodisiac and adaptogenic properties (*Panax quinquefolius* L., *Panax ginseng* C.A.Mey.), for wound healing (*Panax ginseng* C.A.Mey.), for positive effects in amnesia, cognitive behaviour and/or anxiety (*Panax ginseng* C.A.Mey., *Albizia lebbeck* (L.) Benth.) and for many other activities (Sparg et al., 2004).

Notably, there is a close relationship between inflammation and cancer. e.g., inflammation may result in oncogenesis, and tumor-promoting inflammation can lead to cancer metastasis (Hanahan, et al., 2000). However, inflammation is not only associated with oncogenesis. It may also be involved in other disorders, such as colitis (Mahmoud et al., 2021), neurotoxicity (Hussein et al., 2018), etc. Thus, the underlying mechanisms of inflammation and cancer were discussed individually for a variety of potential molecular targets.

The questionable clinical efficacies: limited number of studies, often of low quality

Though flavonoids and saponins have attracted much attention, few of these compounds have undergone clinical studies and even fewer have yielded marketed drugs.

Clinical efficacies inferred from meta-analysis and systematic reviews

To evaluate the available evidence about the efficacies of flavonoids and saponins for different treatment conditions, a comprehensive search for eligible systematic reviews and meta-analyses in the Cochrane Library was performed. The quality of evidence reflects the extent to which we are confident that an estimate of the effect is correct. Although the quality of evidence represents a continuum, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach results in an assessment of the quality of a body of evidence in one of four grades (Di et al., 2020) and are presented in Table 2.

The search yielded a total of 81 items, of which 63 correspond to flavonoids and 18 to saponins. Ten studies involving 2 meta-analyses and 6 systematic reviews for flavonoids and 1 meta-analysis and 1 systematic review for saponins were selected for this analysis. A summary of all meta-analyses and systematic reviews, giving information about the participants, intervention, comparison, and outcome (PICO) model and quality of evidence of each study is shown based on GRADE in Table 3. In this Table 3 and subsequent tables, all retrieved flavonoids and saponins are presented, regardless of their possible *"pain"* status.

FLAVONOIDS have been reported to prevent or treat different conditions, including chronic disorders (Robertson et al., 2020), cancer and colorectal neoplasms (Filippini et al., 2020; Jin et al., 2012), venous insufficiency and venous leg ulcers (Martinez-Zapata et al., 2020; Scallon et al., 2013), acute cerebral infarction (Cao et al., 2008), age-related macular degeneration (Evans, 2013), and haemorrhoids (Perera et al., 2012) (Table 3).

In these systematic reviews and meta-analyses, flavonoids have been assessed for their antioxidant (Evans, 2013; Robertson et al., 2020), anticancer (Filippini et al., 2020; Jin et al., 2012), phlebotonic (Martinez-Zapata et al., 2020; Perera et al., 2012; Scallon et al., 2013), and neuroprotective (Cao et al., 2008) effects.

Flavonoids as antioxidants. Two studies (Evans, 2013; Robertson et al., 2020) examined the efficacy and safety of flavonoids from Pine bark and Ginkgo leaves extracts as antioxidants.

Pine bark (*Pinus spp.*) extract is rich in bioflavonoids, predominantly proanthocyanidins, which are antioxidants. Robertson assessed the efficacy and safety of pine bark extract supplements for treating 10 chronic disorders, including asthma, attention deficit hyperactivity disorder, cardiovascular disease, chronic venous insufficiency, diabetes (type I, type II), erectile dysfunction, female sexual dysfunction, osteoarthritis, osteopenia, and traumatic brain injury. Despite the inclusion of 27 RCTs, the certainty of evidence was very low. Robertson could not find any relationship between the intake of pine bark extract supplements and its efficacy due to small sample sizes, limited numbers of RCTs per condition, variation in outcome measures, and poor reporting of the included RCTs. With regards to its safety, no serious adverse events were reported, or, in a few cases, were not assessed; non-serious adverse events were gastrointestinal disturbances and headache. Then the current available evidence is not sufficient to support claims regarding Pine bark benefit or to assure its safety in the 10 chronic conditions investigated. It is recommended that future trials select outcomes clinically relevant to people and measured in a standardised way. In addition, well-designed, adequately powered and well-reported RCTs of pine bark extract supplements are necessary.

Table 2
Quality of evidence GRADE system

GRADE	DEFINITION
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Source: GRADE Handbook

Table 3
Summary of Meta-Analysis and Systematic Reviews for flavonoids and saponins based on the PICO model.

Type of study	Participant (N)	Intervention	Comparison	Outcome	Quality of evidence (GRADE)	Reference
FLAVONOIDS AS ANTIOXIDANT						
Meta-Analysis including 27 RCTs	10 Chronic disorders: Asthma, Attention deficit hyperactivity disorder, Cardiovascular disease, Chronic venous insufficiency, Diabetes (type I, type II), Erectile dysfunction, Female sexual dysfunction, Osteoarthritis, Osteopenia, Traumatic brain injury. (1641)	Diaberet tablet (**pycnogenol**, vit E, coenzim Q) Enzogenol capsule (*Pinus radiata*, **proanthocyanidins**) Flavangenol (*Pinus maritima*, oligomeric **proanthocyanidin**) IDIProst capsule (*Serenoa repens* + pine bark extract + Zn^{++}) Lady Prelox capsule (L-arginine HCl, L-citrulline, rose hip extract (*Rosa canina*), **pycnogenol**) Oligopin capsule (*Pinus pinaster*, **procyanidins**) OPC-3 sachet (**Pycnogenol**, grape seed, bilberry, citrus, and red wine) Prelox tablet (**Pycnogenol**, L-arginine) **Pycnogenol** capsule (*Pinus maritima/pinaster*, **procyanidins**) **Pycnogenol** capsule + powder on ulcerated area	Placebo tablet Placebo sachet Placebo capsule Standard ulcer care *Serenoa repens* Placebo capsule	Decrease in asthma symptoms Participants off albuterol inhaler Inattention and hyperactivity assessed with CAP, CTSR and CPRS scores Diastolic blood pressure HDL and LDL cholesterol Pain scores Disappearance of pain Microcirculation-related symptom scores Visual acuity Diabetic peripheral neuropathy symptom score IIEF-5 score IIEF erectile function domain score FSFI satisfaction domain score FSFI pain domain score Composite WOMAC score Change in NSAIDs and COX-2 inhibitor usage Bone alkaline phosphatase Cognitive failure questionnaire scores Rivermead post-concussion symptom questionnaire scores	Very low	(Robertson et al., 2020)
FLAVONOIDS AS ANTIOXIDANT						
Systematic review including 2 RCTs	Age-related macular degeneration (AMD) in one or both eyes (119)	Maidenhair tree (*Ginkgo biloba*) extract (24 % **ginkgo-flavone glycosides** + 6 % terpenoids) Maidenhair tree (*Ginkgo biloba*) extract (25 % **ginkgo-flavone glycosides** + 6 % terpenoids)	Placebo No intervention	Number of participants with disease progression Number of participants with new visual loss due to AMD	Not conclusive	(Evans, 2013)
FLAVONOIDS AS ANTICANCER						
Meta-Analysis including 142 RCTs, case-control and cohort observational studies	Gastrointestinal cancer: oral, pharyngeal, laryngeal, oesophageal, stomach, liver, pancreatic, biliary tract, and colorectal Respiratory tract cancer: nasopharyngeal, lung, and mesothelioma Breast cancer Urogenital tract cancer: prostate, endometrial, ovarian, renal, and urinary Haematological cancer: haematopoietic, leukaemia, lymphoma, and multiple myeloma	Green tea (*Camellia sinensis*) extract (rich in **catechins, epigallocatechin-3-gallate (EGCG)**) supplementation Green tea extract (**EGCG**) capsule Drinking green tea Highest green tea exposure	Placebo Lowest green tea exposure	Number of participants developing cancer (incidence) Number of participants dying from cancer (mortality)	Low to very low	(Filippini et al., 2020)
FLAVONOIDS AS ANTICANCER						
Systematic review s including 8 prospective cohort design, case-control study and RCT	Colorectal cancer and colorectal adenomas (390,769)	**Total flavonoids** Individual flavonoids: **Isoflavones** (biochanin A, daidzein, formononetin, genistein) **Flavonols** (quercetin, kaempferol, myricetin, isorhamnetin) **Flavones** **Flavan-3-ols** (catechin, epicatechin) **Flavanones** (naringenin, hesperetin) **Anthocyanins**	NI	Incidence of colorectal cancer Colorectal adenomas	No clear evidence	(Jin et al., 2012)

(*continued on next page*)

Table 3 (*continued*)

Type of study	Participant (N)	Intervention	Comparison	Outcome	Quality of evidence (GRADE)	Reference
FLAVONOIDS AS ANTIOXIDANT						
FLAVONOIDS AS PHLEBOTONIC						
Systematic review including 69 RCTs	Chronic venous insufficiency (7690)	Natural flavonoids: French maritime pine bark extract (*Pinus maritima*, **procyanidins**) Grape seed extract (*Vitis vinifera*, **procyanidins**) Ruscus (*Ruscus aculeatus,* **rutoside**), **hesperidin** capsule **Rutoside** **Hidrosmine** **Diosmine** (micronised) + **hesperidin** capsule Disodium flavodate Natural **Saponosides** *Centella asiatica* tablet Synthetic: Calcium dobesilate Naftazone Aminaftone Chromocarbe	Placebo tablet Placebo capsule	Oedema in the lower legs (dichotomous variable) Oedema in the lower legs (calf and ankle circumference, mm) Quality of life scales (Chronic Venous Insufficiency International Questionnaire) Ulcer healing	Moderate to low	(Martinez-Zapata et al., 2020)
FLAVONOIDS AS PHLEBOTONIC						
Systematic review including 9 RCTs	Venous leg ulceration (1075)	Micronised purified flavonoid fraction: **Diosmin** + **hesperidin** tablet + local treatment + compression bandaging Hydroxyethylrutosides: **Hydroxyethylrutosides** tablet + compression bandaging + local therapy High dosage of **troxerutin** + standard compression + local therapy	Placebo tablet Placebo tablet + local therapy + compression bandaging Compression bandaging Local topical therapy	Number of ulcer healed Changes in ulcer surface area Time to achieve complete healing	Very low	(Scallon et al., 2013)
Systematic review including 24 RCTs	Haemorrhoidal disease (2344)	Natural phlebotonic: **Bioflavonoids (quercetin, rutin, hesperidin, rutosides** (**troxerutin**, buckwheat herb extract, *Ruscus aculeatus*), **diosmin, hidrosmin**, ginkgo biloba; **saponosides** (**escin** from horse chestnut seed extract) Synthetic phlebotonic: calcium dobesilate naftazone aminaftone chromocarbe Others: iquinosa, flunarizine, sulfomucopoly-saccharide Phlebotonic + lifestyle changes (fiber) or topical treatment Phlebotonic + non-operative or surgical treatment	Phlebotonic (non-flavonoids) Placebo Conservative management (lifestyle intervention, high fiber diet) Lifestyle changes (fiber) or topical treatment (fiber) + placebo Lifestyle changes (fiber) or topical treatment Non-operative or surgical treatment + placebo Non-operative or surgical treatment	Measurements of pain Measurements of bleeding Measurements of pruritus	High to moderate	(Perera et al., 2012)
FLAVONOIDS AS NEUROPROTECTIVE						
Systematic review including 9 RCTs	Acute cerebral infarction (723)	Dengzhanhua (*Erigeon breviscapus*, **scutellarin**) injection + routine treatment	Routine treatment	The proportion of patients with market neurologic improvement	No clear evidence	(Cao et al., 2008)
SAPONINS AS ANTIDIABETIC						
Meta-Analysis including 10 RCTs	Diabetic retinopathy (754)	Ruscus (*Ruscus aculeatus* L., **ruscogenine**) extract tablet Sanqi Tongshu capsule, Xuesaitong and Xueshuantong injections (*Panax notoginseng*, **sanchinoside**) **Puerarin** (*Pueraria lobata*) injection Tetramethylpyrazine injection	Placebo Troxerutin tablet Mecobalamin Oxerutins No treatment Conventional intervention or surgical treatment	Progression of retinopathy Visual acuity Reduction in microaneurysms Observations in retina HbA1c (%)	Low to very low	(Zhang et al., 2018)

(*continued on next page*)

Table 3 (*continued*)

Type of study	Participant (N)	Intervention	Comparison	Outcome	Quality of evidence (GRADE)	Reference
FLAVONOIDS AS ANTIOXIDANT						
SAPONINS AS ANTIPLATELET						
Systematic review including 8 RCTs	Acute ischaemic stroke (660)	Sanchitongshu (*Panax notoginseng*, **sanchinoside**) capsule + aspirin Naoming injection Xuesaitong soft capsule Sanqitongshu capsule Xuesaitong + low molecular dextran Xueshuantong injection + co-intervention	Placebo + aspirin No intervention Solcosery Co-intervention Low molecular dextran	The proportion of participants with neurological improvement (MESSS score) Barthel index score	No clear evidence	(Chen et al., 2008)

Abbreviations N: number; RCT: Randomised controlled trial; NSAIDs:nonsteroidal anti-Inflammatory drugs; COX-2: cyclooxygenase-2; NI: not ndicated; CAP: child attention problems; CTRS: Conner's Teacher Rating Scale; CPRS: Conner's Parent Rating Scale; HDL: high-density lipoprotein; LDL: low-density lipoprotein;: IIEF: International Index of Erectile Dysfunction; FSFI: Female Sexual Function Index; WOMAC: Western Ontario and McMaster Universities; HbA1c: glycated haemoglobin A1c; MESSS: Modified Edinburgh-Scandinavian Stroke Scale .

Ginkgo biloba extracts, known for antioxidant properties, contain two families of constituents (ginkgo-flavone glycosides and terpenoids). Evans, 2013 determined the effect of a *Ginkgo biloba* extract on the progression of age-related macular degeneration (AMD) and evaluated any potential harmful effects. Given that only two small trials have suggested possible benefit of *Ginkgo biloba* on vision, the quality of evidence was not conclusive. None of these reviews have identified serious major adverse effects. Only one study reported a headache, blood in the stools and abdominal pain as minor adverse effects. Future trials should be larger, and last longer, in order to provide a more robust measure of an eventual effect of Ginkgo extract on AMD.

Flavonoids as anticancer agents. Two reviews (Filippini et al., 2020; Jin et al., 2012) investigated the association between green tea consumption and dietary flavonoids as anticancer agent.

There is a high consumption worldwide of green tea (*Camellia sinensis*), which contains catechins, a powerful antioxidant family of compounds. Laboratory studies have suggested that catechins may inhibit cancer cell proliferation. Filippini examined the association between green tea consumption and the reduction of different types of cancer (gastrointestinal, respiratory tract, breast, urogenital tract and haematological). Findings from experimental and nonexperimental epidemiological studies yielded inconsistent results, thus providing a low to very low quality of evidence for beneficial effects of green tea consumption on reducing the overall risk of cancer or on specific cancer sites. The studies also indicated the occurrence of several side effects associated with high intakes of green tea. Some evidence of beneficial effects of green tea at some cancer sites emerged from the RCTs and from case-control studies, but their methodological limitations, such as the low number and size of the studies, and the inconsistencies in the results of cohort studies, limit the interpretability of the Risk Ratio estimates. In addition, the majority of included studies were carried out in Asian populations characterised by a high intake of green tea, thus limiting the generalisability of the finding to other populations. Well-conducted and adequately powered RCTs would be needed to associate possible beneficial effects of green tea consumption on cancer risk.

Flavonoids (Fig. 1), have many possible biological effects that may play a role in cancer prevention. Jin determined an association of the intake of total flavonoids and main flavonoid subclasses, with colorectal neoplasms including colorectal cancer and adenomas. Unfortunately, there is no clear evidence regarding flavonoid intake, which is difficult to determine, and the prevention of colorectal neoplasms. The findings of reduced risk of colorectal cancer or adenoma recurrence, for some flavonoid subclasses and individual flavonoids, were not reliable because of methodological weaknesses. The doses of flavonoids and ranges of follow up varied significantly, so that the effective dose and treatment prior to flavonoid ingestion was unclear.

Flavonoids as phlebotonic agents. Three studies (Martinez-Zapata et al., 2020; Perera et al., 2012; Scallon et al., 2013) evaluated the efficacy and safety of flavonoids as phlebotonic agents.

Natural flavonoids extracted from plants and similar synthetic products may improve blood circulation. These products are collectively known as venoactive or phlebotonics. Martinez-Zapata assessed the efficacy and safety of phlebotonics administered orally or topically for treatment of signs and symptoms of lower extremity chronic venous insufficiency (CVI). Zapata concluded that there is *(i)* moderate-certainty evidence that phlebotonics probably slightly reduce oedema, compared to placebo; *(ii)* moderate-certainty evidence of little or no difference in Quality of Life; and *(iii)* low-certainty evidence that these agents do not influence ulcer healing. Moderate-certainty evidence suggests that phlebotonics are probably associated with a higher risk of adverse events than placebo. Studies included in this systematic review provided only short-term safety data; therefore, the medium- and long-term safety of phlebotonics could not be estimated. Findings for specific groups of phlebotonics are limited, due to small study numbers and heterogeneous results. Additional high quality RCTs focusing on clinically important outcomes are needed to improve the evidence base.

Micronized Purified Flavonoid Fraction (MPFF), the most extensively studied flavonoid formulation, and hydroxyethylrutoside (HR), also known as troxerutin, have been reported for efficacy in venous ulcer healing. Scallon evaluated the clinical effects of flavonoids, both MPFF and HR, on the healing of venous leg ulcers. There is some evidence to show that flavonoids can help heal venous leg ulcers, however, it is not possible to ascertain whether the apparently beneficial effects were real or not. There is some evidence that MPFF caused significantly more adverse events (mild to moderate) than control treatments, including skin changes (eczema) and gastrointestinal disturbances (diarrhoea). This result needs to be interpreted cautiously, as most of these trials were poorly reported, and so had an unclear risk of bias for randomisation, allocation concealment, blinding and methods for addressing incomplete outcome data. Larger and better conducted trials are needed to assess the true clinical effect of flavonoids for treating venous leg ulcers.

Perera suggests that there is a potential benefit in treating the signs, symptoms and severity of haemorrhoidal disease with natural and synthetic phlebotonics, as well as a benefit in alleviating post-haemorrhoidectomy symptoms. Outcomes such as bleeding and overall symptom improvement show a statistically significant beneficial effect and there were few concerns regarding their overall safety from the evidence presented in the clinical trials. However methodological limitations were encountered, and more robust clinical trials that consider these limitations will need to be performed in the future.

Flavonoids as neuroprotective agents. Only one review (Cao et al., 2008)

assessed whether Dengzhanhua preparations are effective and safe at improving outcomes in patients with acute cerebral infarction. Dengzhanhua (breviscapine) injection, a crude extract of several flavonoids obtained from *Erigeron breviscapus* (Vant.), a Chinese traditional herbal drug for cardiocerebral vascular diseases recorded by the Chinese Drug Dictionary 1977 edition. The main active components of Dengzhanhua injection are stated to be scutellarin (a glycoside flavone) and pyromeconic acid (a pyranone derivative). Although treatment with dengzhanhua injections appeared to improve neurological function, there was no evidence that treatment improved the chance of being alive and free of disability. Further well-designed trials, with high methodological quality and large sample size are needed.

SAPONINS have been investigated for diabetic retinopathy (Zhang et al., 2018), and acute ischaemic stroke (Chen et al., 2008), acting as antidiabetic and antiplatelet, respectively (Table 3).

Saponins as antidiabetic agents. Zhang et al, 2018 conducted a meta-analysis, including 10 RCTs, for evaluating the effectiveness and risk of single herbal medicines (Ruscus extract tablet, Sanqi Tongshu capsule, tetramethylpyrazine, Xueshuantong, Xuesaitong, and Puerarin injections) for diabetic retinopathy. The Sanqi Tongshu capsule, Xueshuantong injection and Xuesaitong injection all include an extract of Radix Notoginseng (*Panax notoginseng* (Burkill) F.H.Chen ex C.Y.Wu & K.M.Feng.), one of the most widely used medicinal herbs in China, and the main ingredients were sanchinosides. There was no substantial evidence to support or refute the use of some single herbs to treat diabetic retinopathy from the current available evidence. It was difficult to exclude the placebo effect as a possible explanation for observed differences due to the lack of placebo control in the included studies. Further adequately designed trials are needed to establish eventual evidence. Specifically, Ruscus extract, Radix Notoginseng (Sanqi), tetramethylpyrazine and puerarin remain stated as potentially promising agents.

Saponins as antiplatelet agents. Chen et al, 2008 assessed the ability of Sanqi extracts to increase disability-free survival in patients with acute ischaemic stroke. Sanqi (Radix Notoginseng) appears to be beneficial and safe for acute ischaemic stroke in this review, but the small sample and inferior quality of studies prevented a definite conclusion. There is no clear evidence to suggest the benefit of Sanqi as antiplatelet agent. More well-designed randomised controlled trials are required.

Clinical efficacies inferred from randomised clinical trials (RCTs)

To comprehensively review the clinical efficacy of flavonoids and saponins, 12,719 publications for flavonoids and 5,439 for saponins were retrieved in online databases, from 1990 to 2022. After screening, only 32 studies on flavonoids and 4 on saponins could be included for summarizing and analysing (Fig. 4). In summary, flavonoids had clinical efficacy on chronic venous insufficiency (Cesarone et al., 2010a; Cesarone et al., 2006a, b; Cesarone et al., 2010b; Petruzzellis et al., 2002), cervical lesions (Ahn et al., 2003), diabetes (Cesarone et al., 2006c), perennial allergic rhinitis (Yoshimura et al., 2007), external anogenital warts (Tatti et al., 2008), bacterial prostatitis (Cai et al., 2009), facial aging (Chuarienthong et al., 2010; Furumura et al., 2012), menopausal symptoms (Agosta et al., 2011), Sanfilippo syndrome (de Ruijter et al., 2012), angina pectoris (Luo et al., 2012), male pattern hair loss (Loing et al., 2013), early stage chronic lymphocytic leukemia (Shanafelt et al., 2013), benign prostatic hyperplasia (Suardi et al., 2014), ulcerative colitis (Rastegarpanah et al., 2015), light-chain amyloidosis (Choi et al., 2016N), cystic fibrosis (Berkers et al., 2020), traumatic cerebral infarction (Lubo et al., 2020), and mucopolysaccharidosis type III (Ghosh et al., 2021), whilst saponins had efficacy on venous oedema in chronic deep vein incompetence (Diehm et al., 1992), male erectile dysfunction (Choi et al., 1995), acute impact injuries (Wetzel et al., 2002), and systemic lupus erythematosus (You et al., 2009) (Tables 4 and 5).

Conclusions and recommendations for future research on clinical efficacy

Flavonoids are probably the bioactive compounds most often associated with varied biological activities (antioxidant, anticancer, treating chronic venous insufficiency, neuroprotective, treating cervical lesions, antidiabetes, antiallergic rhinitis, etc.). While several biological effects have also been ascribed to saponins (analgesic, anti-nociceptive, antioxidant, antifungal, antidiabetic, antiplatelet, treating venous oedema and male erectile dysfunction, etc). To give an overview of the importance imparted to flavonoids and saponins, the medicinal plants referred in Russian Pharmacopoeia (14th edition), Chinese Pharmacopoeia (2020 Ed), and European Pharmacopoeia, that are standardized by the content in these chemicals are presented in Suppl. Tables S5-S9.

Overall, only 10 meta-analyses and systematic reviews (involving 290 interventional and observational studies), and 36 clinical studies on flavonoids and saponins, revealed that further high-quality investigations are warranted (Tables 3-5).

More robust clinical trials appear needed to further support the use of flavonoids and/or saponins in preventing or treating chronic disorders, cancer and colorectal neoplasms, age-related macular degeneration, venous insufficiency, venous leg ulcers, haemorrhoids, acute cerebral infarction, diabetic retinopathy, and acute ischaemic stroke conditions.

Limitations of the bibliographic research strategy applied here

We noted the low retrieval of papers on some highly investigated plants, notably ginseng. This is probably due to a descriptor sometimes/often missing in published papers; as many authors dealing with these plants do not mention "saponins" in their abstract, keywords or paper, this chemical indexation is probably missed out by database indexers. Although interesting and important, a review on such specific herbs is however out of the scope of the present review. Regarding ginseng itself, an assessment report by the European Medicines Agency's herbal committee (HMPC, 2014) indicates that many of the points discussed in the present paper are valid; even for this highly-investigated plant, the Committee concludes that: *"Despite the fact that numerous clinical studies investigating the pharmacological properties of Panax ginseng have been conducted since the 1980s, several systematic reviews reveal that data is still inconclusive and strong evidence for clinical efficacy cannot be deduced"*.

It is advisable that the following recommendations be kept in mind regarding future clinical trials:

1) **Selection** of compounds worthy to study clinically should be based *(i)* on high-quality *in vitro* and *in vivo* studies, controlled for their power in detecting clinically translatable effects and for their sensitivity to interferences and bias; and *(ii)* a good *a priori* knowledge of bioavailability and biotransformation parameters.
2) **Clinical trials** should be large enough, last longer and clearly describe the method of random number generation and allocation concealment. Before starting a study, appropriate registration provides a fulfilment of ethical obligations to participants and the research community, information to potential participants and referring clinicians, reduction of publication bias, etc.
3) **Participant** numbers should be estimated by the proper statistical method to detect true treatment effects. Criteria should be included to minimize the variation of characteristics among participants. Blinding participants should also be necessary, as well as good reporting of methodology and losses of participants.
4) **Intervention** variability is high, especially in the investigated natural extracts and compounds. The use of similar or identical agents as well as therapeutic regimes should be considered in studies. The doses of flavonoids or saponins and ranges of follow up are important, so the effective dose and treatment prior to intervention should be clear. The intervention should be designed to study pure compounds or fully characterized mixtures and compare outcomes with a placebo group.

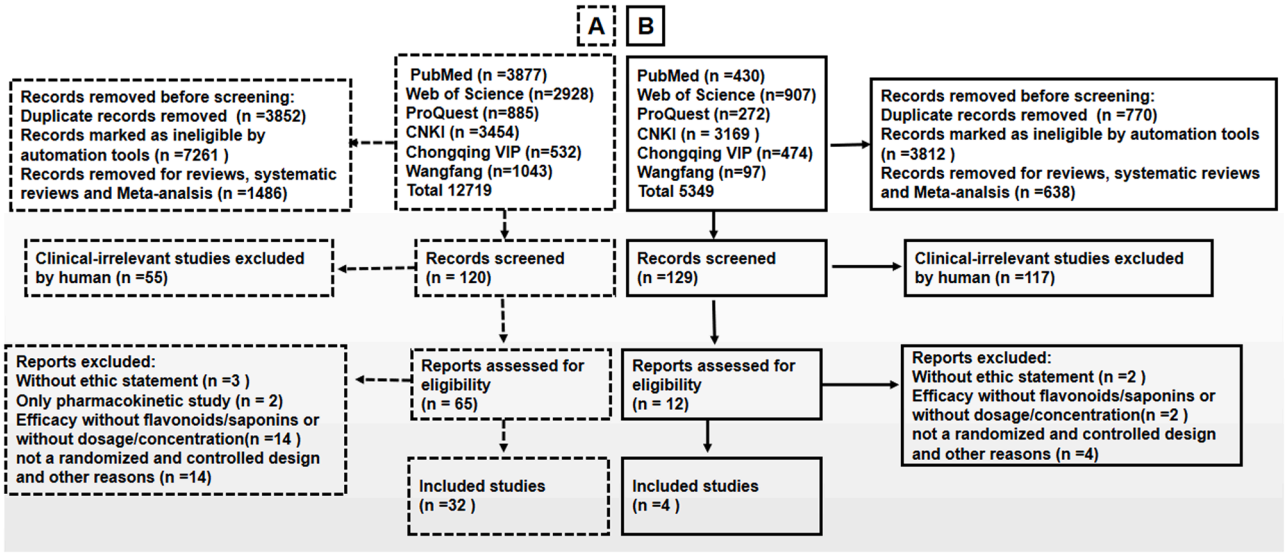

Fig. 4. Efficacy of flavonoids and saponins in clinical studies retrieved from PubMed – workflow diagram of data collection. Access date: May 14, 2022. A: flavonoids; B: saponins.

5) **Comparison** of the main alternative or gold standard with the intervention is necessary. Selection of adequate comparison will help ensure comparability of treatments at baseline.
6) **Outcomes** should be selected as objective and clinically relevant to people and measured in a standardised manner. Suitable endpoints for outcome measures should be chosen appropriately.
7) **Long term follow-up** studies are needed to better define the safety profile and more clearly outline the risk/benefit ratio. Establishment of a clear monitoring and reporting system for the adverse effects of interventions should be taken into consideration.
8) Finally, it is highly recommended that all studies comply with the CONSORT (www.consort-statement.org/) statements in reporting results.

The challenges of toxicology

Although flavonoids and saponins widely exist in nature and daily diets, and possess extensive biological activities, some of them can be toxic or even fatal. They and their secondary metabolites may result in hepatotoxicity, nephrotoxicity, and even injuries to multiple organs. For example, bavachin, a prenylated flavanone from Fructus Psoraleae (fruit of *Psoralea corylifolia* L.), increases the levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in serum. The liver cell injury is accompanied by IL-1β secretion in a drug-induced liver injury (DILI) mouse model (Qin et al., 2021). In addition, many flavonoids (bavachin, corylifol A, neobavaisoflavone, isobavachalcone, and bavachinin) have inhibitory effects on UGT1A1, which is an important cause of hepatotoxicity related to *Psoralea corylifolia*, including elevated bilirubin level and liver injury (Wang et al., 2015). On the other hand, some saponins present in common herbs, such as *Melia azedarach, Bupleurum* root and *Euphorbia* herb, induce injuries to liver, kidney testis and hematologic system. Major toxicities suspected or averred for flavonoids and saponins are listed in Table 6, and the mechanisms illustrated in Fig. 5.

The challenges of complex mixtures: Synergism

Quite often, complex formulas are vaunted for "synergistic" or "detoxification" purposes, but supporting experimental data are scarce in the literature.

The term "synergy" originates from the Greek word *"συνέργος"*, which means *"working together"*. In other words, the combination of several compounds in complex mixtures is supposed to produce a synergy, i.e., an enhancement of activity. Classically, synergy is defined as *"Yogavahi"* in the Ayurveda *"Charak Samhita"* to mean *"the one that fortifies the efficacy and safety of others in the results of combining ingredients"* (Mukherjee et al., 2018); a similar philosophy underpins many polyherbal formulas, for example in traditional Chinese medicine (Yang et al., 2014). Phytotherapy effectively relies on complex mixtures of compounds, either from a single herb or, more often from different herbs, most probably leading to interactions, a major challenge in their study. As drug interactions include four types, addition, synergism, potentiation, antagonism, the combination index (CI) was introduced for quantifying synergy in binary mixtures (Chou, 2006); a CI = 1 indicates additive, CI < 1 indicates synergistic, and CI > 1 is evidence of antagonistic effect between the tested compounds (Hanahan and Weinberg, 2000).

Recently, a new sense has been proposed for the term *"synergy"* to design network interactions of two or more compounds that lead to qualitatively new pharmacological effects that cannot be produced by any single component, regardless of dose (Panossian et al., 2018).

Although synergistic activity has been frequently invoked and/or reported in phytomedicine, it is *"faster to say, than to prove"* such effects (Verpoorte et al., 2018).

Synergism in the field of flavonoids and nearby polyphenols

We have reviewed the literature with the aim to find the articles in which synergistic effects of flavonoids and nearby polyphenols were measured and quantified.

It was reported that quercetin combination with some tetrose, pentose, and hexose-derived carbohydrates enhanced the radical scavenging effects by 75% (Belaya et al., 2019). The synergistic effect of the mixture related to the number of hydroxyl substituents and the presence of aldehyde or ketone groups in carbohydrate molecules. This can be explained since, firstly, when dissolved in water, quercetin transforms into a tautomeric diketo form where hydrogen bonds form between its carbonyl groups and hydroxyl groups of the monosaccharide, promoting the formation of molecular complexes, improving the solubility of the flavonoid in water with a synergistic effect. Secondly, reducing carbohydrates are able to restore oxidized forms of quercetin, which is confirmed by the great synergistic effect of aldose in comparison with ketoses, regardless of the number of hydroxyl groups in the molecule. The synergistic effect of the quercetin–monosaccharide compositions, established in a model reaction with a hydrazyl radical, was compared to

Table 4
Efficacy of flavonoids in clinical studies retrieved from PubMed (Access date: May 14, 2022).

No.	Flavonoids	Disease	Dosage	Treatment group			Placebo/control group			P value	References
				Patients	Ratio Male/female	Efficacy rate %	Patients	Ratio Male/ female	Efficacy rate %		
1.	O-(β-hydroxyethyl)-rutoside	Chronic venous insufficiency	1000 - 3000 mg, b.i.d.	40	4/36	82.5	20	6/14	30	< 0.01	(Petruzzellis et al., 2002)
2.	(-)-epigallocatechin-3-gallate (EGCG)	Cervical lesions	200 mg, topically used	51	NA	69 (35/51)	39	NA	10 (4/39)	< 0.05	(Ahn et al., 2003)
3.	Flavonoids	Chronic venous microangiopathy	50 mg, t.i.d.	21	11/10	Progressive decrease in skin flux; significant decrease in capillary filtration; significant improvement in the symptomatic score; reduction in edema	18	NA		< 0.05	(Cesarone et al., 2006b)
4.	Pycnogenol (flavonoids); Daflon (diosmin, hesperidin, and other flavonoids)	Chronic venous insufficiency	Pycnogenol 50 - 100 mg, t.i.d; daflon 500 mg, b. i.d.	86	NA	improved	NA	NA	NA	NA	(Cesarone et al., 2006a)
5.	Flavonoids	Diabetic microangiopathy	50 mg, t.i.d.	30	18/12	improved	30	16/14		< 0.05	(Cesarone et al., 2006c)
6.	Naringenin, chalcone	Perennial allergic rhinitis	360 mg/d	17	7/10	improved	16	7/9		< 0.05	(Yoshimura et al., 2007)
7.	Catechins	External anogenital warts	sinecatechins ointment 15% and 10%, topical use	321	159 (74M/85F) (ointment 15 %) and 162 (79M/83F) (ointment 10%)	78.4% (ointment 15%) 74.0% (ointment 10%)	83	41/42	51.50	< 0.001	(Tatti et al., 2008)
8.	Quercitin	Bacterial prostatitis	460 mg/d	106	NA	89.60	prulifloxacin 37	NA	27	<0.0001	(Cai et al., 2009)
9.	O-(β-hydroxyethyl)-rutoside	Chronic venous insufficiency	1000 - 2000 mg/d	NA	NA	improved	NA	NA	NA	< 0.05	(Cesarone et al., 2010a)
10.	Flavonoids	Chronic venous insufficiency and microangiopathy	50 mg, t.i.d.	67	Pycnogenol 33 (18M/15F) and Pycnogenol+ compression 34 (19M/15F)	improved	compression 31	16/15	NA	< 0.05	(Cesarone et al., 2010b)
11.	Flavonoids	Wrinkles	topical use gel, b. i.d.	20	0/20	improved	NA	NA	NA	0.05	(Chuarienthong et al., 2010)
12.	Isoflavones Lignanes (from *Magnolia*)	Menopausal symptoms	60 mg	300	0/300	improved	334	0/334	NA	NA	(Agosta et al., 2011)
13.	Genistein	Sanfilippo disease	10 mg/kg/d	10	10/5	improved	15	10/5		0.03	(de Ruijter et al., 2012)
14.	Flavonoids	Photoaged facial skin	40 - 100 mg/d	112	112F (100 mg for 24 women vs. 40 mg for 88 women)	improved	NA	NA	NA	< 0.05	(Furumura et al., 2012)
15.	Puerarin	Angina pectoris	100 mg/d	194	104/90	88.14%, 171/194	194	102/92	61.86 (120/ 194)	< 0.05	(Luo et al., 2012)
16.	total isofl avone ≥ 98% and biochanin (phytoestrogen flavonoid) a ≥ 12%	Male pattern hair loss	5%	15	15/0	improved	15	15/0	NA	< 0.05	(Loing et al., 2013)
17.	epigallocatechin gallate (EGCG)	Early-stage chronic lymphocytic leukemia (cll)	2000 mg, b.i.d.	42	30M/12F	69(29/42)	NA	NA	NA	< 0.05	(Shanafelt et al., 2013)
18.	Quercetin	Benign prostatic hyperplasia	1 tablet	18	18/0	improvement in voiding function		18/0	NA	0.3	(Suardi et al., 2014)

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Table 4 (*continued*)

No.	Flavonoids	Disease	Dosage	Treatment group			Placebo/control group			P value	References
				Patients	Ratio Male/female	Efficacy rate %	Patients	Ratio Male/ female	Efficacy rate %		
19.	Flavolignanes	Ulcerative colitis	140 mg/d	38	17/21	92	38	13/19	65	0.5	(Rastegarpanah et al., 2015)
20.	Apigenin	Ultraviolet A (315–400 nm)-induced cytotoxicity	2 g, topical use	20	0/20	improved in skin evenness, moisture content and TEWL	20	0/20	NA	< 0.001	(Choi et al., 2016N)
21.		Chronic venous disorders (cvd)	500 - 1000 mg/d	571	83/488	MPFF 1000-mg oral suspension had similar efficacy to MPFF 500-mg tablet, and similar safety to two 500-mg tablets	568	79/489	NA	NA	(Carpentier et al., 2017)
22.	Panduratin A (chalcone derivative)	Skin Hydration, gloss, and wrinkling	200 mg/kg/d	NA	NA	improved	NA	NA	NA	NA	(Kim et al., 2017)
23.	EGCG	Light-chain amyloidosis	126 mg, t.i.d.	36	16/20	improved	21	8/13	NA	NA	(Meshitsuka et al., 2017)
24.	Flavonoid fraction	Symptomatic chronic venous disease	1000 mg/d vs. 500 mg b.i.d.	87	16/71	improved	87	NA	NA	NA	(Kirienko et al., 2019)
25.	Genistein	Cystic fibrosis (cf)	3.3 and 5.0 mg/ Kg/d	14	6/8	no effects on mutated cystic fibrosis transmembrane conductance regulator (CFTR) protein	16	11/5	improved	< 0.05	(Berkers et al., 2020)
26.	Quercetin	Diabetic foot ulcer	0.2%, topical treatment	28	14/14	reduced the wound healing time	28	14/14	NA	< 0.01	(Gallelli et al., 2020).
27.	Puerarin	Traumatic cerebral infarction (tci)	400 mg/d, i.v.	28	19/9	82%	24	18/6	61%	< 0.05	(Lubo et al., 2020)
28.	Genistein	Sanfilippo syndrome (mucopolysaccharidosis type iii)	160 mg/kg/d	9	NA	no effects	11	NA	NA	0.26	(Ghosh et al., 2021)
29.	2% of total flavonoid content per capsule	Type 2 diabetes	300 mg/d	45	14/31	improved	35	9/26	NA	< 0.01	(Tonelli et al., 2022).
30.	Quercetin	Type 2 diabetes	500 mg/d	36	0/36	reduced systolic blood pressure significantly but had no effect on other cardiovascular risk factors and inflammatory biomarkers	36	0/36	NA	=0.01 and < 0.0001	(Zahedi et al., 2013)
31.	Quercetin	Healthy mild hypercholesterolemia adults	100 ml/d (≧ 200 mg/dl)	12	NA	improved	12	NA	NA	< 0.05	(Lu et al., 2015)
32.	Quercetin	Non-alcoholic fatty liver disease (NAFLD)	500 mg, b.i.d.	39	24/15	improved	39	26/13		< 0.05	(Pasdar et al., 2020)

Note: b.i.d.: twice a day; t.i.d.: three times a day; i.v.: intravenous injection.

Table 5
Efficacy of saponins in clinical studies retrieved from PubMed (Access date: May 14, 2022).

No.	Saponins	Disease	Dosage	Treatment group			Placebo/control group			*P* value	References
				Patients	Ratio Male/female	Efficacy rate %	Patients	Ratio Male/female	Efficacy rate %		
1	Escin	Venous edema in chronic deep vein incompetence	NA	40	NA	NA	NA	NA	NA	NA	(Diehm et al., 1992)
2	Ginseng saponins	Erectile dysfunction	1200 mg/d for 3 months	18	18/0	66.7	25	NA	28 (7/25)	< 0.05	(Choi et al., 1995)
3	Escin	Acute impact injuries	1% - 2%	105	71/34	87.6 (92/105)	51	NA	29 (15/51)	0.0002	(Wetzel et al., 2002)
4	Ginsenosides	Systemic lupus erythematosus	50 mg/day	28	2/28	89.28	NA	NA	66.67	< 0.05	(You et al., 2009)

Note: b.i.d.: twice a day; t.i.d.: three times a day; i.v.: intravenous injection.

that in the autoxidation process of cottonseed oil. In the reaction with the peroxy radicals of cottonseed oil, the synergistic effect of the quercetin monosaccharide compositions increases up to 300% only for sugars capable of reducing quercetin radicals and reacting with air oxygen, reducing the steady-state concentration of peroxy radicals in the system (Belaya et al., 2019).

The antioxidant activity of the mixture of phenolics and resveratrol determined by the Briggs–Rauscher (BR) reaction is presented. Although the t_{inhib} for gallic acid was about nine-fold lower than for quercetin, it was almost the same for their combinations with resveratrol (Skroza et al., 2015). A considerable synergistic effect (137.8%) was established for the binary combination of gallic acid and caffeic acid (Hajimehdipoor et al., 2014).

Hidalgo et al. have screened eleven flavonoids (cyanidin-3-O-glucoside, malvidin-3-O-glucoside, delphinidin-3-O-glucoside, peonidin-3-O-glucoside, pelargonidin-3-O-glucoside, catechin, epicatechin, kaempferol, myricetin, quercetin, and quercetin-3-β-glucoside) and their mixtures for antioxidant efficacy (Hidalgo et al., 2010). The mixture of epicatechin and quercetin-3-β-glucoside displayed the highest synergistic effect, whereas myricetin with quercetin resulted in an antagonistic effect.

The mixture effect (ME) is one of the common approaches for expressing the synergistic or antagonistic effects occurring between pairs of antioxidants in a mixture (Peyrat-Maillard et al., 2003; Pozharitskaya et al., 2015). To investigate ME, solutions of ascorbic acid and phloroglucinol and their mixtures were prepared and their ability to scavenge the DPPH• radical was studied. The antioxidant activity for a model mixture of ascorbic acid and phloroglucinol showed that they have a strong synergistic effect on the reaction with the DPPH• radical (ME = 2.99). The EtOH extract from *Fucus vesiculosus* had a pronounced synergistic effect (ME 2.03) (Obluchinskaya et al., 2021).

However, unfortunately, the problems for the mixture research are that the most commonly used method for the quantification of flavonoids and nearby polyphenols synergistic effects relies on *in vitro* testing of antioxidant activity. We could not find papers in which synergy of these compounds was proven and calculated in *in vivo* experiments. Such studies are certainly required for a better understanding of this phenomenon and its applications to drug development.

Synergism in the field of saponins

Synergistic interactions between conventional antibiotics (ciprofloxacin, kanamycin, and cefixime), and a classical antifungal (fluconazole), and saponin extracts from *P. argentea* and *S. marginata* were tested using the checkerboard essay method. Synergy between antibiotics and saponins-rich extracts at low concentration (fraction of the MIC:MIC/4) was studied using microdilution assay. 50 µl of the saponins-rich extracts at MIC/4 were added to microwells containing, separately, 50 µl of antibiotics or antifungal dilutions (Wei et al., 2021b). For bacterial strains, 30 combinations were studied, 17 (56.7%) combinations had synergism, 7 (23.3%) had additive effect, 4 (13.3%) had no effect and 2 (6.7%) had antagonistic effect. For *Candida* strains, 8 combinations of saponins extracts and fluconazol were tested. All of these combinations (100%) exhibited a synergism with FIC ranging from 0.31 to 0.50).

The combined antibacterial activity of the hederagenin-based sapindoside A, sapindoside B and sapindoside C, from *Sapindus mukorossi* Gaertn., was studied against seven bacteria, alone and in combination (Wei et al., 2021a). However, only the combination of sapindoside A and sapindoside B synergistically inhibited the growth of *Micrococcus luteus* (Kurin et al., 2012). Saponins-rich extracts at low concentration (fraction of the MIC: MIC/4) combination with antibiotics exhibited a synergism with FIC ranging from 0.31 to 0.50 (Wei et al., 2021b). In another study, sapindosides A and B synergistically modified the fatty acid compositions and membrane fluidity of *Cutibacterium acnes* by interaction with the bacterial type II fatty acid synthesis, sapindoside A playing a major role in the synergy (Wei et al., 2021c).

The fungicidal saponin CAY-1 extracted from Cayenne pepper, was used in microdilution studies where CAY-1 and amphotericin B (AB) or itraconazole were mixed with non-germinated and germinating conidia of three species of *Aspergillus* and *Candida albicans*. Inhibition was determined visually after 24 and 48 h (De Lucca et al., 2006). It was found that CAY-1 had a synergistic interaction only with AB against *C. albicans*. Moreover, the synergistic effect decreased by a third from 24 to 48 h.

The *in vitro* antifungal activities of *Camellia* (Theaceae) saponins (TS) and mancozeb against *Pestalotiopsis theae* was studied (Yang and Zhang, 2012), indicating that the combined treatment of TS and mancozeb (3:7) exhibited synergistic antifungal interaction against both mycelial growth and spore germination, with cotoxicity coefficient values largely exceeding the significancy value of 100.

In cancer cells, notably, most combinations with saponins synergistically increased cytotoxicity, stressing the importance of synergy in a multi-target drugging approach, often revendicated in phytotherapy.

Liquid chromatography-mass spectrometry allowed the identification or preliminary determination of 28 glucuronide oleanane-type triterpenoid carboxylic acid 3,28-bidesmosides along with 6 monodesmosides in the root extract of *Gypsophila trichotoma* Wender (Gevrenova et al., 2019). The tested gypsogenin-based saponins had a C-28 ester chain substituted with acetyl, cis/trans-methoxycinnamoyl, and acetyl and sulfate groups. In the presence of non-cytotoxic concentrations of acetylated saponins (20 µg/ml), a strong synergy was observed, on normal mouse fibroblasts (CCL-1 cell line) and lymphoma cells, between saponins (Voutquenne-Nazabadioko et al., 2013) and between saponins and etoposide (Gevrenova et al., 2019). The etoposide IC_{50} was reduced from 98 to 20 µg/ml when combined with saponins; apoptosis was evidenced by caspase activation, increased levels of cytosolic mono- and oligonucleosomes, and nuclear fragmentation, together with a marked increase in ROS generation.

On several cell lines, the cytotoxic monodesmosidic steroidal saponin digitonin was combined in non-toxic concentrations (5 µM,

Table 6
The list of flavonoids and saponins leading to toxicity.

NO.	Flavonoids*/saponins#	Affected organ (s)/tissue(s)	*In vitro/in vivo*/clinical study	Dosage /concentration	Mechanisms	References
1	Sodium aescinate #	Cardiovascular	*In vivo*	MNLC: 1.5 and LC_{10}: 2.0 μg/ml	↑ heart malformations, cardiac looping defects and pericardial edema	(Liang et al., 2016)
2	Dioscin #	Gastro-intestinal tract	*In vivo*	300 mg/kg/d	↑ tract distension	(Xu et al., 2012)
3	Saponins	Kidney	*In vivo*	1.5 g/kg (63 mg sapogenin), 3.0 g/kg (126 mg sapogenin)	↑ acute tubular necrosis in the kidneys; ↑ serum creatinine and urea	(Wisløff et al., 2008)
4	Amentoflavone *	Genetics	*In vitro*	0.28 - 1.12 mg/plate	Mutagenicity	(Cardoso et al., 2006)
5	Quercetin * and genistein *	Genetics	*In vivo*	270 - 302 mg/kg	↑DSB and MLL gene;	(Vanhees et al., 2011)
6	Ginsenoside Re #	Hematology	*In vivo*	38, 113, 375 mg/kg/d	↑ fibrinogen, corpuscular volume and corpuscular hemoglobin; ↑ activated partial thromboplastin time, and neutrophils reticulocyte count	(Lu et al., 2012)
7	Saponins	Hematology	*In vivo*	NOAEL of DFS: 100 mg/kg/d for maile and 200 mg/kg/d for female	↑ WBC; ↓ MCHC	(Lan et al., 2015)
8	20(S)-ginsenoside Rg3 #	Hematology	*In vivo*	NOAEL: 7.20 mg/kg/d	↑ WBC and neutrophils, ↓ lymphocytes	(Liu et al., 2011)
9	Saponins	Kidney	*In vivo*	NA	↑ tubular necrosis	(Collett et al., 2011)
10	Amentoflavone, sciadopitysin, ginkgetin, isoginkgetin and bilobetin *	Kidney and Liver	*In vitro* and *in vivo*	*In vitro*: IC_{50} 10 - 100 μg/ml; *in vivo*: 20 mg/kg	↑ ALP and BAX	(Li et al., 2019c)
11	Chrysin *	Kidney and Liver	*In vivo*	1000 mg/kg; LD_{50}: 4350 mg/kg	↑ hepatic and renal oxido-nitrosative stress; ↓ hematology; ↑ albumin, bilirubin, ALT, AST, creatinine, and GGT	(Yao et al., 2021)
12	Crude saponins	Kidney and Liver	*In vivo*	NOAEL: 50 mg/kg/d	↓ blood sugar, ↓ liver and kidney metabolism	(Zhang et al., 2022a)
13	Saponins	Kidney, Liver and testis	*In vivo*	LD_{50}: 500 mg/kg	↑ cytoplasmic eosinophilia and densely stained nuclei of the liver, tubular necrosis of the kidney, presence of ill-defined testes	(Abere et al., 2010)
14	Bavachin *	Liver	*In vitro* and *in vivo*	*In vitro*: 2.5 - 10 μM; *in vivo*: 25 mg/kg.	↑ IL-1β and caspase-1; ↑ROS;	(Qin et al., 2021)
15	Bavachin, corylifol A, neobavaisoflavone, isobavachalcone, and bavachinin *	Liver	*In vitro*	IC_{50}: 12.51 μg/ml	↓ UGT1A1	(Wang et al., 2015)
16	Toosendanin *	Liver	*In vitro* and *in vivo*	*In vitro*: 50 μM; *in vivo*: 3.75, 7.5 or 15 mg/kg.	↑ ENOA and ROS	(Zhuo et al., 2021)
17	Saikosaponins #	Liver	*In vivo*	4675, 7925, 12957, 21650 and 36075 mg/kg	↑ AST, ALT and LDH; ↑ CYP2E1; ↑ ROS.	(Li et al., 2017a)
18	Dioscin B *	Liver	*In vitro* and *in vivo*	*In vitro*: 200 μM; *in vivo*: 75, 150, 200 mg/kg.	↑ P450 3A	(Wang et al., 2017)
19	Amentoflavone *	Liver	*In vitro*	IC_{50}: 0.12 - 16.81μM	↓ UGTs (UGT1A1, 1A3, 1A4, 1A6, 1A7, 1A8, 1A9, 1A10, 2B4 and 2B17)	(Lv et al., 2018)
20	Sciadopitysin *	Liver	*In vitro*	IC_{50}: 0.20 - 1.34 μM	↓ UGTs (UGT1A1, UGT1A3, UGT1A8, and UGT1A10)	(Wang et al., 2016)
21	20-O-β-d-glucopyranosyl-20(S)-protopanaxadiol (Compound K) #	Liver	*In vivo*	NOAEL: 6.7 mg/kg/d	↑ ALT, γ-GT, and ALP	(Gao et al., 2011)
22	Pterocephin A #	Liver	*In vitro* and *in vivo*	*In vitro*: 2, 4 and 8 μM; *in vivo*: 60 - 120 mg/kg	↑ ALT and AST; ↑ Ca^{2+} and ROS, ↑ RIP1 and NF-κB	(Wang et al., 2021b)
23	Vicenin-1 *	Mortality	*In vivo*	LD_{50}: 4837.5 mg/kg	NA	(Kandhare et al., 2016)
24	Ginsenoside Re #	Reproduction	*In vitro*	0.05 mg/ml	↓ median morphological score, somites and yolk sac diameter	(Chan et al., 2004)
25	Flavonoids and saponins	Reproduction	*In vivo*	200 mg/ml	potential insecticide	(Men et al., 2022)
26	Flavonoids	Reproduction	*In vivo*	LC_{50}: 353 mg extract/10 g fly diet	↓ GST-activity, survival-rate, and emergence of young fruit flies	(Pam et al., 2021)
27	Quercetin *	Reproduction	*In vitro*	5000 – 200000 μM	↓ Ca^{2+}-ATPase and ↓ sperm motility	(Khanduja et al., 2001)
28	Flavonoids	Reproduction	*In vivo*	aqueous extract: 47 mg/kg/d; hydroethanolic extract: 35 mg/kg/day	↓ neonatal survival; ↑ biochemical oxidative parameters in maternal (liver, kidney, heart, and hippocampus) and in pups (liver and kidney)	(Moresco et al., 2017)

Note: MNLC, maximum non-lethal concentration; DSB: DNA doublestrand breaks; MLL: rearrangements in the mixed-lineage leukemia; NOAEL: no-observed-adverse-effect level; ALT: alanine aminotransferase; γ-GT: Gamma-glutamyltranspeptidase; ALP: alkaline phosphatase; ↓: decrease, inactivation or reduction; ↑: increase, activation or induction; NA: not available.

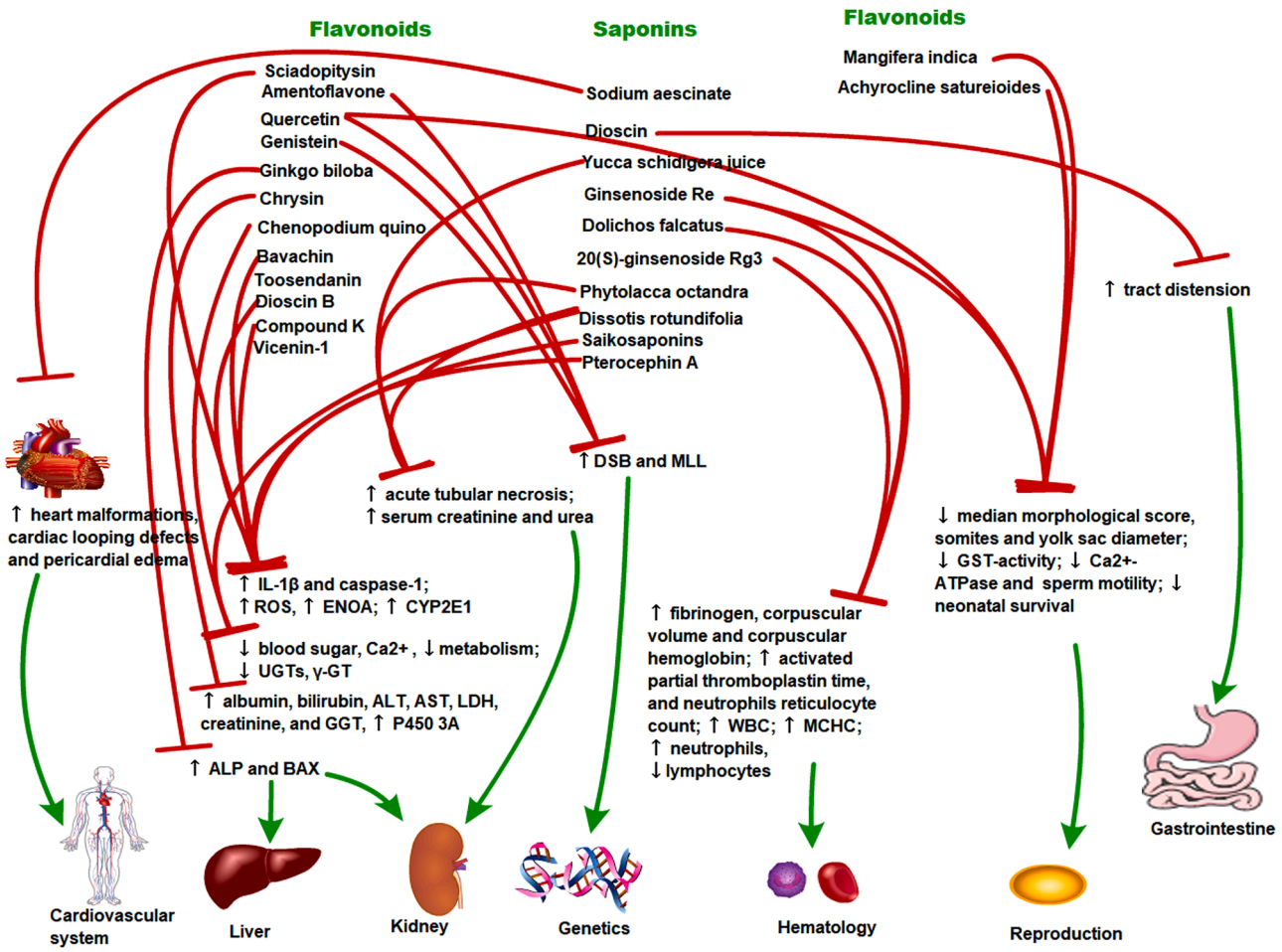

Fig. 5. Toxicological effects of some flavonoids and saponins. ↓: decrease, inactivation or reduction; ↑: increase, activation or induction.

except 2 μM for MCF-7) with different phytochemicals, including phenolics, terpenoids, and alkaloids, to evaluate potential synergistic or additive effects. An enhanced cytotoxicity was observed in most combinations. Even multi-drug resistant (MDR) cells (such as CEM/ADR5000 cells), with a high expression of P-glycoprotein, were responsive to combinations. Sanguinarine was the most cytotoxic alkaloid against CEM/ADR5000, MCF-7, and CCRF-CEM cells, both alone and in combination with digitonin; as compared to sanguinarine alone, the combination was 7- to 45-fold more cytotoxic (Eid et al., 2012).

A synergistic study showed that the monkey fibroblasts-derived Cos7 cells were extremely sensitive to the combinations between monodesmosidic saponins (aescin, digitonin, glycyrrhizic acid, *Quillaja* saponins) and monoterpenes (α-pinene, thymol and menthol), lowering IC_{50}s by a factor of 10 to 100 (Herrmann and Wink, 2011).

As is the case for flavonoids, *in vivo* studies are crucially missing to detail the real effects of saponins combinations.

An additional area that warrants studies resides in the emulsifying effects of saponins that probably help in solubilizing other lipophilic compounds, modifying their pharmacokinetics. Here again *in vivo* data are sorely lacking.

The challenges of complex mixtures: detoxification

Besides synergism, some antagonisms between phytochemicals, notably those involving flavonoids and saponins, could also be useful for detoxification. The challenge is how to highlight such useful interactions/detoxifications from a complex mixture.

Liquiritin and isoliquiritin of *Glycyrrhiza uralensis* Fisch. (Glycyrrhizae Radix et Rhizoma), which is often used in Traditional Chinese Medicine formulas for detoxification (Li et al., 2019b), reduce the concentration of aconitine (active compound in Aconiti Lateralis Radix Praeparata) in the formula Sini Tang by forming a complex with the alkaloid, therefore reducing the toxic effects of aconitine to negligible (Peter et al., 2014). The formula appears safer for clinical use, which was shown by an *in vivo* study of improvement of early ventricular remodelling and cardiac function after myocardial infarction in a rat model (Liu et al., 2014). Aconite alkaloids are alkaline, while the sapogenin glycyrrhizic acid is acidic, the toxicity of aconite significantly decreases when Aconiti Lateralis Radix Praeparata and Glycyrrhizae Radix et Rhizoma are decocted together, probably due to an acid-base neutralization, i.e., the formation of a polar ion pair (He et al., 2019a). The same effect reduces the bioavailability of *Coptidis chinensis* Franch. rhizoma (Huanglian) alkaloids, (Li et al., 2017b), reducing extracted amounts, solubility, and dissolution of berberine (Chan et al., 2020). He et al. also clarified potential detoxification mechanism of licorice that up-regulates efflux transporters to reduce absorption of xenobiotics across small intestinal membrane (He et al., 2019a). The detoxification effects of repeated doses of Glycyrrhizae Radix et Rhizoma are mediated mainly via the induction of drug metabolizing enzymes and efflux transporters (Li et al., 2019b).

What has been missed so far and is there a need to go further?

Flavonoids and saponins have attracted a growing number of researches in the last two decades compared to other natural products, e.g., alkaloids, anthraquinones or steroids (Fig. 3 and Table 1). However, it is striking to note that 11 flavonoids and 3 saponins are listed in the top 39 compounds reported as *"pains"*, indicating that a critical data-

driven approach is needed to differentiate real and *"pain"* effects (Bisson et al., 2016). Interestingly, the top 39 *"pains"* also include taxol, a compound most effective for treating cancer (Bisson et al., 2016). Capuzzi also reported that 87 small molecule FDA-approved drugs contained *"pains"* alerts (Capuzzi et al., 2017). Thus, despite any *"pains"* aspects, the real value of flavonoids and saponins as potential new drugs cannot be excluded.

Flavonoids: effects other than antioxidant

Besides anti-oxidative stress, some clinical efficacies of flavonoids has been recorded for cancer, chronic venous insufficiency, cervical lesions, diabetes, rhinitis, dermatopathy, prostatitis, menopausal symptoms, angina pectoris, male pattern hair loss, lymphocytic leukeamia, gastrointestinal disease, traumatic cerebral infarction, and so on (Table 2). The biological mechanisms underlying these effects are, however, still poorly understood. As the pandemic of COVID-19 has been leading to a severe global health issue since 2020, drug development and pharmacological research are currently focused on preventing and treating COVID-19, notably with natural products. For example, baicalein and baicalin, the flavonoids known for effects on cerebral vascular disease (Yuan et al., 2020), cancer (Kiatwuthinon et al., 2021; Li et al., 2020) and other diseases (Xu et al., 2021), have been reported interesting as they inhibit SARS-Cov-2 3CL protease (3CLpro) (Su et al., 2020). They may also be of potential value in preventing fibrosis-related chronic damage underlying long COVID-19, given their well-defined antifibrotic activities (Zhou et al., 2022).

Progress in the study of drug interactions from the application of OMICs and in silico screening

A well-designed drug interaction can be very useful to enhance drug effects and/or decrease its toxicity. Fucofuroeckol-A, a phlorotannin isolated from brown alga *Eisenia bicyclis* increases the effects of erythromycin and lincomycin to inhibit *Propionibacterium acnes* (Lee et al., 2014). Actually, an important issue which should not be ignored is that most of medicinal herbs, as well as Chinese medicine formulas, consist of a number of active compounds, supposed to exert synergistic effects, leading to higher effects at very low dosages (Wang et al., 2021a; Yu et al., 2013). Such subtleties may yield novel insights in drug development; although difficult to decipher, complex interactions can probably be resolved through an application of OMICs, e.g., genomics, transcriptomics, metabolomics, proteomics, lipidomics and glycomics, and *in silico* virtual screening, i.e., molecular docking or network pharmacology. For example, the integration of transcriptomics and metabolomics showed that the combination quercetin-resveratrol in high-fat diet fed mice enhances processes of glycolysis and fatty acid oxidation and suppresses gluconeogenesis (Zhou et al., 2012). Another example was shown for *Cannabis sativa* L., a most common illicit drug that leads to cardiovascular risk, including myocardial infarction, angina and arrhythmias. *In silico* virtual screening indicated that genistein, a soybean isoflavone, believed to pass the blood–brain barrier (Fuloria et al., 2022), may inhibit the binding of the major *Cannabis* toxin, Δ^9-tetrahydrocannabinol (Δ^9-THC), to the cannabinoid receptor 1 (CB1/CNR1) (Wei et al., 2022).

The interactions between phytochemicals and the intestinal microbiota

Another critical factor influencing phytochemical effects is associated with their metabolism in the gut (Wang et al., 2019). For example, di-hydroxyphenyl-γ-valerolactone, a major gut metabolite of flavan-3-ols (a flavonoid class abundant in grapes, blueberries, strawberries, raspberries), was shown to prevent the adhesion of THP-1 monocytes to endothelial cells in a dose-dependent manner (Lee et al., 2017). Similarly, bioactions of ginsenosides have been attributed to their gastrointestinal metabolites (Yang et al., 2020). These data indicate promising researches of such phytochemicals via metabolism in guts.

Also, the interactions between flavonoids/saponins and the intestinal microbiota metabolism [notably in *Fusobacterium, Eubacterium, Bifidobacterium, Flavobacterium, Microbacterium*, and *Rhodanobacter* (Yang et al., 2020)] may be another important issue that has been missed until gut flora was paid more attention to as a *"special human organ"*. These interactions may point to two research directions pertinent to efficacy or toxicity. For example, intestinal microbiota can transform ginsenoside Rb1 to ginsenoside compound K (CK). CK, but not Rb1, shows significant anti-proliferative and pro-apoptotic effects in colorectal cancer cells (Wang et al., 2012). In addition, CK suppresses melanoma cell growth by inducing autophagic cell death, whereas the parent Rb1 fails to show significant effects at the same concentration (Kang et al., 2014). Furthermore, ginsenoside Rg1 (GRg1) was shown to improve Alzheimer's disease symptoms via promoting growth of *Proteobacteria* (Wang et al., 2020). These reports confirm that phytochemicals could play important roles through interacting with specific microbial species.

Conclusions

Available data point to a serious gap in our knowledge of herbal medicines, with crucial links missing between what we know of their phytochemistry and their reported traditional uses.

On one hand, analytical methods are readily available to profile flavonoids and saponins and it's tempting, given the biological activities widely purported for these phytochemicals, to apply them to any investigated herb, bringing even more grist to the mill. On the other hand, the 3Rs strategy now applied in research implies more and more *in vitro* testing, often disconnected from pharmacokinetic realities and susceptible to many artifacts. And finally, the purity of tested compounds is hardly reported, leaving the possibilities of highly active minor contaminants in test material. Also, clinical studies that could confirm/infirm the relevance of flavonoids and saponins are often missing or of low quality.

Despite these limitations in our knowledge, flavonoids and saponins may have potential roles to play in the prevention and treatment of various diseases. More careful *in vitro, in vivo* and clinical studies, as well as new technologies and approaches are required to eventually prove their value. Thus, flavonoids and saponins still have a long way to go before being confirmed as clinically important agents.

Declarations

Ethics approval and consent to participate
NA.

Consent for publication

The manuscript is read and approved by all authors for publication.

Availability of data and materials

The datasets supporting the conclusions of this article are included within the article and its additional files.

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Authors' contributions

PD: study design; XW, YM, QX, AS, OP, EF, ML, HL, LVM, and PD: data curation, double-checking, data analysis, and section contribution; WX, PD, and QX: manuscript revision.

Conflicts of interest

Given his role as Editorial board member, Alexander N. Shikov was not involved in the peer-review of this article and has no access to information regarding its peer-review.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.phymed.2022.154580.

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