REVIEW ARTICLE

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# Flavonoids as a library of privileged structures – what are the gains?

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## ABSTRACT

**Background:** Flavonoids constitute the main, and biogenetically uniform category of plant phenolics, which are ubiquitous and recognized as minor and non-nutrient food components, which can significantly influence human health; e.g. their pronounced anti-oxidative properties are believed to be beneficial through inhibiting inflammatory processes. Although great many contemporary drugs are derived from natural sources, primary from plant secondary metabolites these sources of inspiration are relatively seldom discussed in context of growing demand for new medicines needed to battle current epidemics.

**Methods:** A need for interdisciplinary discussion on natural product constituents which are present in recommended human diet is brought up, since their metabolic, epigenetic and pharmacological effects, which can be summarized as a life style factor, are likely to be no less important for human well-being than pharmacological intervention after a diagnosis. Example of flavonoid sub-categories compounds, such as flavanols, catechins and isoflavones, which are present in everyday food and beverages are discussed in terms of their biological activities and mechanisms of their pharmacological action, also in view of their possible role as new drug leads and new drug candidates.

**Conclusions:** Natural products, such as flavonoids, feature some health beneficial activities, which are notoriously difficult to exploit for pharmaceutical purposes, because of their low bio availabilities and rapid metabolism. Recently, combined effort of medicinal and synthetic chemistry has succeeded in demonstrating how fruitful the inspiration of privileged flavonoid structures can be for drug design and development.

**Keywords**

Flavonoids, Glycosides, Drug design, Drug development, Chemical synthesis, Natural products, Nutraceuticals, Pharmacology, Polypharmacology, Systems biology

**Abbreviation**

ADMET: Absorption, Distribution, Metabolism, Excretion and Toxicity; API: Active Pharmaceutical Ingredients; FLAV: Flavonoids; GT: Green Tea; GTP: Green Tea Phenolics; MB: Metabolism; NP: Natural Products; PD: Pharmacodynamics; PK: Pharmacokinetics; PP: Polypharmacology; R&D: Research and Development; SB: Systems Biology; SM: Secondary Metabolites.

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## Introduction

Natural Products (NP) in general and higher plant Secondary Metabolites (SM) in particular, exploited as ethnomedicines since dawn of humanity, continue to serve as an indispensable source of active compounds for modern drug design and development, successfully competing with such sophisticated contemporary technologies as combinatorial chemistry and high-throughput screening [1-3]. This remarkable success of the relatively limited resources of structural diversity, numerically estimated at over 210 thousand compounds collection, in comparison to multimillion sets resulting from combination of synthetic compounds databases (ca. $10^8$ molecules), and perhaps infinite number of structures contained in the entire virtual chemical space (>$10^{60}$ compounds can be predicted even for small molecules with MW<500 D only) [4,5], obviously call for serious reflection, particularly in view of relatively poor performance experienced in recent decades by the big pharma environment [6,7]. Let us observe that contemporary populations are exposed to increasing number of unmet medical needs, which surface through growing population pressure, uneven wealth distribution, epidemic growth of indices connected with so called civilization ailments, such as cardiovascular diseases, diabetes, metabolic syndrome, cancer, and neurodegenerative conditions. Currently, it is estimated that less than 15 thousand individual chemical compounds categorized as API (Active Pharmaceutical Ingredients) are used as medicines and are responsible for existence and manufacturing of countless pharmaceutical preparations, differing in dosage, pharmaceutical form and composition. Remarkably, ca. 50% of these compounds come directly, or are derived through relatively minor chemical modifications from the natural products resources. Since apparently, we can cope with exploitation for medicinal chemistry chemical structure databases much better than other, the question of what are "privileged structures" and how to deal with them to optimize drug discovery R&D outcome should be the recurrent topic of investigation. We have observed an extensive accumulation of new knowledge concerning biological activity of NP, as well as an emergence of new concepts in life science domain, such as systems biology, proteomics, epigenetics, metabolomics and finally network pharmacology, radically different from classical concept of a single macromolecular target for a drug lead or drug candidate [8,9]. Consequently, we have undertaken a short review aimed at depiction of a representative and significant group of NP (SM) in a process of evaluation of their roles in nutrition, disease prevention and health protection, taking flavonoids as example, for their widespread occurrence in vegetable food, fruits, herbs, spices, and dietary supplements [10-12].

### ■ Flavonoids and their various biological roles

Flavonoids (FLAVs; collective name coined up by S. Kostanecki towards the end of XIX century from Latin adjective *flavus* - meaning yellow, for description of arylchromone class of plant pigments) constitute a substantial sub-set of higher plants Secondary Metabolites (SM), which presently evoke wide interest as common constituents of medicinal plants, herbs, spices, fruits and vegetables, therefore becoming significant part of human diet [13-17]. FLAV are categorized biogenetically as phenylpropanoids, principally composed of $C_6$–$C_3$–$C_6$ scaffold, assembled into three-cyclic system (chromone linked to aromatic nucleus, commonly a substituted phenyl ring) of 2- (or 3-) phenylchromone, usually hydroxylated, sometime carrying C-prenyl substituents, and often O- and/or C- glycosylated at various positions. There are several types of low molecular weight FLAV skeletons known, such as flavones (e.g. apigenin 1; luteolin 2), flavanols (e.g. quercetin 3; kaempferol 4), flavan-3-ols (e.g. (+)-catechin 5, (-)-epicatechin 6), isoflavones (e.g. daidzein 7; genistein 8), anthocyanins (flavylium cationic salts e.g. delphidin 9, cyanidin 10), dihydrochalcones (e.g. asebogenin 11, phloretin 12), chalcones (e.g. butein 13, xantohumol 14), and aurones (e.g. aureusidin 15, hispidol 16) **(Figure 1)**. More condensed systems like biflavones and condensed tannins, being of lesser interest for medicinal chemistry as not compatible with Lipinski's rule, are omitted in this survey.

Origin of all flavonoids stems from shikimate pathway, combined with acetogenin trail, which is shared by majority of vascular plants. Both: biogenesis of FLAV and their various functions in host plants (phytoalexins, photo-screens, optical atractants, herbivore deterrents, etc.) as well as their significance for allelopathic environmental interactions are relatively well understood [14,16]. In order to discuss an influence of FLAV on mammalian physiology, and ultimately on human health, further

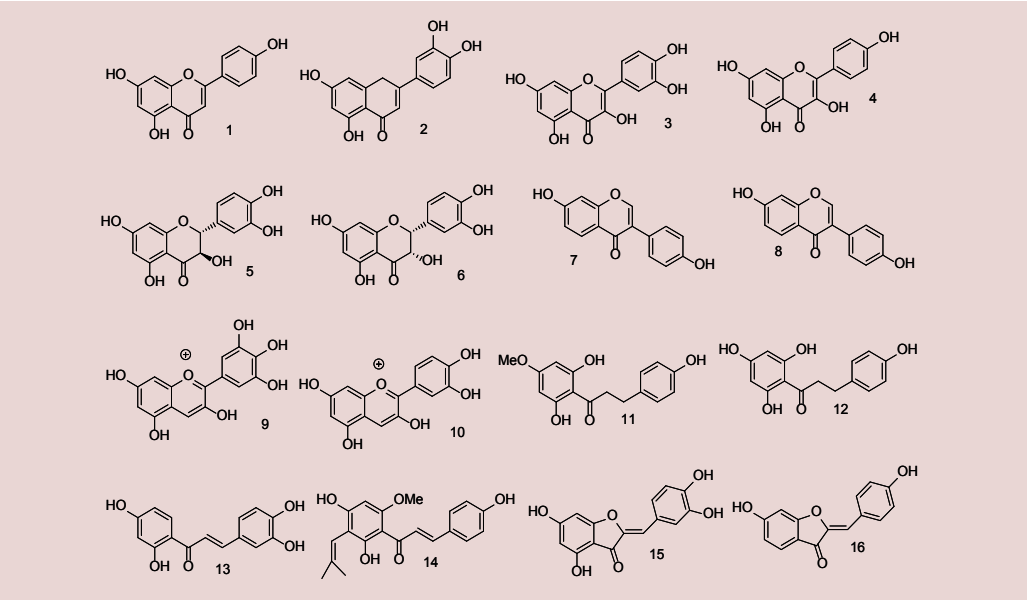

**Figure 1. Typical low molecular weight flavonoids isolated from vegetable sources.**

comments on structure and biological activities of the non-nutrient constituents of ingestible plant materials are necessary. There is little doubt that most numerous phytochemicals in plant derived food belong to polyphenols category, which is much wider subset of natural products than FLAV. Although practically all flavonoids contain a structural element of an aromatic ring substituted with at least one hydroxyl group (known as phenol function), which renders these compounds rather specific chemical reactivity, it has to be considered that non-FLAV phenolics are more widespread and that such sought after feature of food resources as an antioxidant capacity is more often connected with such constituents as phenolic carboxylic acids, stilbenes, xanthones, quinones, coumarins, lignans, and other compounds outside of phenylpropanoid class [18,19]. Strict chemical structural divisions are not always observed in pharmacological studies reports. In fact, NP biological activity experiments often describe catechins or anthocyanes, which are typical flavonoids, as plant phenolics. Therefore, care should be exercised to distinguish reasoning concerning phenolic-rich food and feed effects, from pharmacology of FLAV, studied as individual chemical entities according to schemes designed for biologically active substances of synthetic origin. Since contemporary nutritional sciences strongly recommend vegetable rich diet, FLAV compounds not only became subjects of food supplementation in the Western countries but many of them also entered research programs along the drug discovery line, albeit with very limited success. As a rule, various FLAV performed well on the molecular pharmacology level, but limited bioavailability along with rapid conjugative metabolism leading to systemic excretion were to be blamed for lack of efficiency observed in clinical experiments. It should also be pointed out that FLAV known for dynamic encounters with many targets fit rather poorly the classical pharmacology paradigm postulating one kind of selective interaction of a ligand with specific macromolecular target as the basis for observed biological and pharmacological effects.

Systems Biology (SB) is currently at the beginning of its way towards complete description of the life phenomena as a network of biochemical processes, organized for sustenance of supporting metabolic transformations around regulation of growth, proliferation and reproduction of known forms of life. Remarkably, all recent efforts to define, describe and develop algorithms of systems biology [20,21], although not yet entirely successful, have managed to engage chemistry as the central science for description of such various disciplines of life sciences as physiology, pharmacology, medicine, genetics, biotechnology, agrochemistry, metabolism, bacteriology, biogenesis, food sciences and nutrition, in terms of molecular structures and their transformations within a cell environment. Life is a realm of biomacromolecules like nucleic acids (e.g. DNA) and proteins (e. g. enzymes), which act as a soft matter devices and assemblies, fueled with energy providing molecules (sugars,

nucleotides, lipid phosphates, etc.), to carry around and process relatively smaller organic molecules of primary (essential) and secondary (supportive) metabolism as well as nutritional and non-nutritional food constituents. The new SB interpretation of biochemical networks naturally exert strong influence on description of processes which involve interactions of given biological systems with xenobiotic substances. This calls for a new look conveniently descried as network pharmacology, which is aiming at accommodating all records involving metabolic (MB) and Pharmacodynamics (PD) interactions, in place of traditional, idealized single "ligand – target" complexing [9,22]. In our opinion, the network pharmacology can draw from both sources: traditional knowledge as ethnopharmacology and modern methodology made available with application of bio chemoinformatic tools, in order to generate new ideas concerning exploitation of NP scaffolds for disease prevention as well as pharmacological intervention.

## ■ Flavonoids in food

An example of FLAV, which are ubiquitous as non-nutritional food constituents and at the same time are postulated as new drug leads for most threatening civilization diseases, seems to be well suited for discussion how nature provided structural diversity can be managed for more useful exploitation towards new biologically active entities. Natural FLAV are generally recognized as anti-oxidants, they are also known for estrogenic, anti-proliferative, anti-tumor, anti-microbial, and anti-inflammatory activities, all of which are qualified as health promoting. More intricate insights, made at the molecular level reveal tens of targets, some common like CYP 450 family of enzymes and in majority of cases selective for FLAV sub-categories or even for individual compounds Nevertheless, declaring flavonoids privileged structures from the point of view of medicinal chemistry and drug design may require some explanation. Arguments for the motion are of considerable strength: similarly to other natural products, flavonoids are by definition validated for biocompatibility. Additionally, as common constituents of traditional as well as modern human diet, they are evolutionary well adapted for interactions with a variety of targets characteristic for mammalian physiology. Indeed, it can be postulated that they fit well the general notion of polypharmacology. This does not mean they represent features required for optimal human pharmacokinetics; often opposite is the case, but from the point of view of hit evaluation they may have several advantages over synthetic candidates. Being already advanced in structural design as prospective biological target ligands, NPs in general and FLAVs are multifunctional compounds and thus good subjects for further library design and synthesis. It should be reminded that FLAV are very often glycosylated, which helps molecule trafficking by both: active and passive biological transport systems. Glycosylation also serves as temporary protection from excretion *via* sulfonyl esters or glucuronides [23,24]. Both physicochemical and biological characteristics of glyosidic NPs can be changed by further derivatization such as next glycosylation or acylation with variety of aliphatic or aromatic carboxylic acid residues. It is generally agreed that FLAV compounds, non-nutrients ingested in considerable quantities with vegetable food, have beneficial effects on human health. Described collectively as nutraceuticals, they are believed (with a strong support of epidemiological data) to exert positive effect on homeostasis and prevent harmful action of Reactive Chemical Species (ROS, RNS) generated under various stressful conditions. Detailed investigation of isolated FLAVs under experimental pharmacology conditions reveal their molecular targets: enzymes (kinases, cytochromes), transporters, transcription factors, signaling pathways, etc. [12,16,18]. Although the presence of FLAV in food is generally perceived as ubiquitous the magnitude of its environmental impact it not always fully appreciated. Certain agricultural crops, which are known for FLAV content on a fraction of percent level, are produced in millions of tons annually: soybeans – 300 million t/y; tea – 2.5 million t/y; with citrus fruits; apples; cocoa; onions; grapes; buckwheat and other, in similar capacities. In consequence, high FLAV content isolates and concentrates (frequently even individual compounds of defined chemical purity) of quercetin, catechins, isoflavones and their glycosides, are marketable commodities, which generate avalanche of nutraceutical preparations on poorly controlled market of dietary supplements. Thus far, natural origin of these compounds is taken for granted, although they are relatively easily available by chemical synthesis. Biotechnological methods of FLAV manufacturing are of considerable potential, but appropriate technical processes are still in early developmental stage [12,18,23].

The daily intake of FLAV ingested with fruits and vegetables may vary from tens of milligrams to even grams depending on individual diet. The most abundant: components of tea called catechins, quercetin and its glycosides present in onion and apples, and isoflavone genistein found in soybeans, may accumulate to daily doses of hundred mg order; so, in general pharmacological and hormetic effects of action from individual FLAV plant constituents could be expected despite of rather poor bioavailability of these compounds [11,13].

Evergreen plant originating from Asia-*Camelia sinensis*-constitute the basis for preparation of one of the most ancient and most widely used beverages in the world: tea. Although several different technologies are applied for commercial preparations, majority ending up as fermented black teas, consumed mostly in the West (ca. 80%) Green Tea (GT) traditionally preferred in Asia and Middle East is recently gaining also significance on the global market, because of evidence of its beneficial influence on human health. GT is characterized by high content of flavonoids, particularly monomeric catechins, which include: epicatechin (EC); Epigallocatechin (EGC); Epicatechin 3-O-Gallate (EGC) and Epigallocatechin 3-O-Gallate (EGCG), as the most abundant constituents **(Figure 2)**.

Other catechins and flavanols, like quercetin, kaempferol and myricetin add up as minor constituents of GT, customarily often collectively described as Green Tea Polyphenols (GTP). A cup of green tea on average contains 80–100 or more milligrams of flavonoids and EGCG accounts for ca. 30% of it. Although these compounds are recognized by very efficient antioxidants [25], and consequently efficacious inhibitors of inflammatory processes [26], their acceptance "as such" in role of compounds suitable for medical intervention is problematic, because of low BA, rapid conjugative MB, and quick excretion from mammalian organisms. Therefore, much effort is invested in modern pharmaceutical formulations of these compounds, allowing for controlled delivery, and chemical derivatization which can change radically physicochemical characteristic, solubility, lipophilicity, and consequently PK of suitably designed derivative with a pro-drug property. Along these ways, long chain fatty acid esters of flavones and catechins are being tested for better PK and PD efficacy [27-29].

## ■ Flavonoids as an inspiration for medicinal chemistry

Availability of individual flavonoids in state of defined chemical purity and in bulk quantities, needed for advanced pre-clinical and clinical studies, vary greatly. Catechins, which are likely to be the most widely and frequently consumed FLAV, because their high content in green tea leaves (ca. up to 5% of the dry mass) and ease of simple hot water extraction method are notorious for low stability and quick degrading and conjugative metabolism. They are prone to epimerization reactions and to oligomerization; both processes can be chemically promoted as

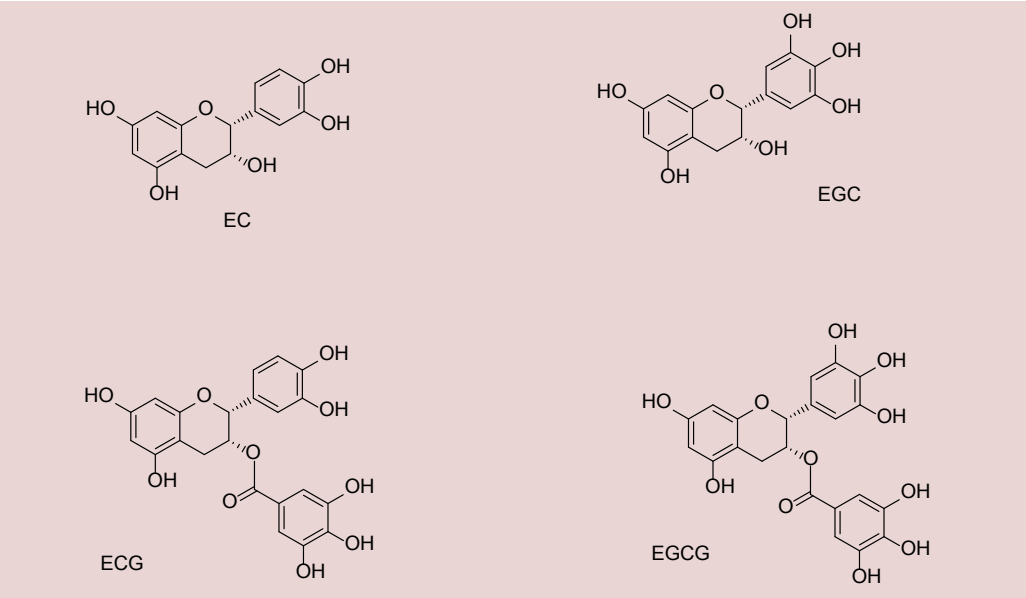


**Figure 2. The main constituents of green tea.**

well as enzyme catalyzed. Studies of mammalian metabolism indicate that catechins are quickly transformed into phenolic acids, particularly protocatechuic acid, which have some intrinsic biological activity. As a result, evidence amassed in favor of beneficial and health promoting action of prolonged intake of catechins in study of anti-inflammatory action or cancer prevention properties are mainly of epidemiological nature. Since it has been found that catechins quickly disappear from blood circulation, a hypothesis has been advanced that slow metabolizers have better chance to benefit from green tea consumption. Despite of considerable advancement of synthetic chemical methods applied to preparation of NPs, relatively low configurational integrity of the two consecutive chiral centers in the saturated C-ring of catechins make them rather difficult target for a chemical preparation process, giving more chance to future biotechnological solutions. At present, chemical derivatization seems to be a likely and viable measure for stability enhancement, with concomitant tune up of biological activity. Thus, EGCG subjected to enzymatic acylation with long chain fatty acid, palmitic acid, affords a mixture of four regioisomeric monoesters, which was investigated as obtained, without separation. Monopalmitic esters exhibited improved stability and bioavailability and performed well in clinical trials designed to check antiviral activity in HIV patients. Similar improvement in chemical stability was observed in monomethylated derivatives of EGCG [27-29].

Quercetin – 3,3'4'5'7-pentahydroxyflavone (3) and its numerous glycosides are likely to be of comparable significance as catechins, for investigation of influence of non-nutrient constituents present in vegetable food upon human wellbeing. Medical interest in flavanols started in 1930s parallel to the antiscorbutic factor studies, when it was realized that they enhance ascorbic acid bioavailability, which rendered them vitamin P status, temporarily. Dietary quercetin comes from consumption of various vegetables but in some contrast to the previously described case, its availability as a bulk chemical is reasonably good, because agrotechnical and biotechnological processes exist for isolation of rutin (disaccharide glucoside: 3-O-quercetin rutinose) from some crops of industrial significance like buckwheat, citrus fruits, apples and onions and its conversion into the flavanol aglycone [29,30]. Owing to advances in analytical methods of separation and detection of NPs, accurate simultaneous determination of flavones, catechins and other phenolics can be developed and validated for a selected plant material in various stages of its processing. Consequently, reliable databases have been elaborated collecting phenolics and flavonoids content of fruits, vegetables, grains, processed foods, dietary supplements and nutraceuticals [31,32]. Quercetin performs well in model experimental studies as compound with antioxidant, antidiabetic, anti-inflammatory, activity but its clinical applications are hampered by relatively poor water solubility (<0.1 g/100 mL at 210˚C) and low bioavailability [33]. Therefore, much attention is devoted recently to elaboration of its efficient delivery systems [34].

Genistein and related isoflavones (daidzein, glycytein, biochanin A, formononetin) differ in type of chromane ring substitution (3-Ph- instead of 2-Ph- ring B junction as consequence of isoflavone isomerase action on chalcone cyclization products) and are much more limited in occurrence than other FLAVs. Isoflavone pharmacology commenced during 1940s with discovery of estrogenic action of clover species constituents, which endangered the sheep husbandry in Western Australia. Proven affinity of genistein to the estrogen receptor beta led to its classification as a phytoestrogen, which in turn inspired many clinical trials aimed at prevention of menopause effects, osteoporosis and inhibition of hormone dependent tumors [35,36]. Genistein is a principal isoflavone of soy, one of the main agricultural crops in the global scale, accumulating in beans on the 2 mg/g level. During raw soybean processing into feed and food, genistein ends up in the protein fraction (together with daidzein and their β-D-glucopyranosides: genistin and daidzin), thus becoming a constituent of a great variety of processed food; which led to some controversial opinions at least in case of baby formula being prepared from soy flour [37]. There are many nutraceutical isoflavone preparations of various compositions on the market and genistein itself has undergone a lot of clinical trials as prospective antiosteoporotic, antiangiogenic, cardiovascular, neuroprotective and antitumor agent, with relatively little progress towards registration as FDA approved drug. Nevertheless, experimental therapies, for example in neurodegenerating glycosaminoglycan plaque storage in children with genetic disorder known as SanFelipe disease are continued [38]. In some contrast to previously described FLAVs genistein is a stable compound,

relatively easily available from natural sources as well as through chemical synthesis, but it shares with other flavonoids poor bioavailability and susceptibility towards both: conjugative and degrading metabolism [35].

## ■ Synthetic modifications of natural flavonoids for new drug design

Each of the above examples, and in principle any of the FLAV with promising biological activity can be a starting point for design of new chemical entities with greatly improved physicochemical properties, which can be a subject of *in silico* search for suitable target or can be obtained by synthesis to undergo regular screening using established biological activity tests for various therapeutic indications. Such postulate is formulated based on a long experience with derivatization based on chemical glycosylation. FLAV are natural products which are very frequently modified by enzymatic glycosylation, facilitating their transport, both: passive and active. While plant physiology employs wide variety of GTS for sugar derivatization and trafficking of their SM, possibility of the phenolic aglycone liberation through reverse reaction–deglycosylation, is always there allowing FLAV to adopt in their natural environment two radically different forms of existence: conjugated–hydrophilic and free aglycone of very limited solubility in cytosolic medium. A state of equilibrium between the two is under constant control and regulated by enzymatic activity [15,23,34]. One type of glyosidic bond: the one with a sugar attached to an aglycon by a carbon–carbon bond is very reluctant to both: chemical and enzymatic cleavage. Consequently, the C-glycosides can serve as biochemical probes of exceptional stability which can mimic some other, more easily cleavable glyosidic conjugates. Natural C-glyosidic compounds are relatively rare but their likely utility for medicinal chemistry was realized with discovery of antibiotic activity of C-nucleosides isolated from aquatic sources [39]. Since that time many chemical synthetic approaches to C-glycosides were designed and perfected [40,41]. Consequently, C-glycosylation can be realistically planned as a derivatization step for any group of NP with the aim of radical modification of its physicochemical properties, pharmacokinetics, metabolism, and finally, pharmacodynamics. Moreover, products of C-glycosylation can be easily subjected to a variety of subsequent derivatization reactions, which would form an array of pro-drugs, which in turn can allow a fine tune up of such molecular parameters as: size, lipophilicity, electron density, charge distribution, water solubility etc. Notably, examples of successful application of C-glycosylation in drug design, and consequently in clinical medicine, based on intrinsic biological activity of natural FLAV already materialized in form of a new generation of oral antidiabetic drugs, which are efficient inhibitors of SGLT2 glucose transporting proteins [42,43]. Interestingly, the FLAV lead – phlorizin, dihydrochalcone D-glucoside was isolated from apple tree root bark already in 1835 and its glycosuria promoting activity was discovered before the end of XIX century [44]. However, it took more than a century to a new generation of efficient drugs based on SGLT2

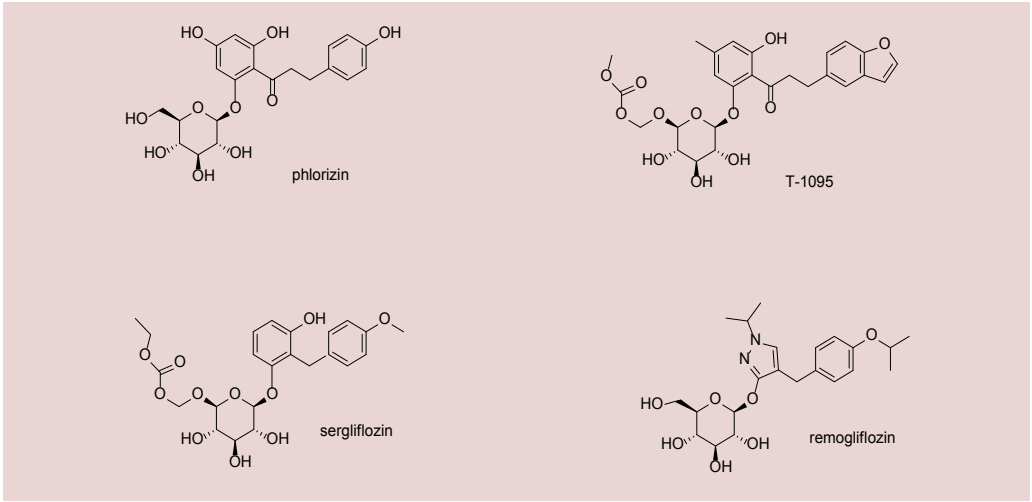


**Figure 3. Natural dihydrochalcone glycoside phloridzin and its synthetic analogs – inhibitors of the SGLT2 glucose co-transporters.**

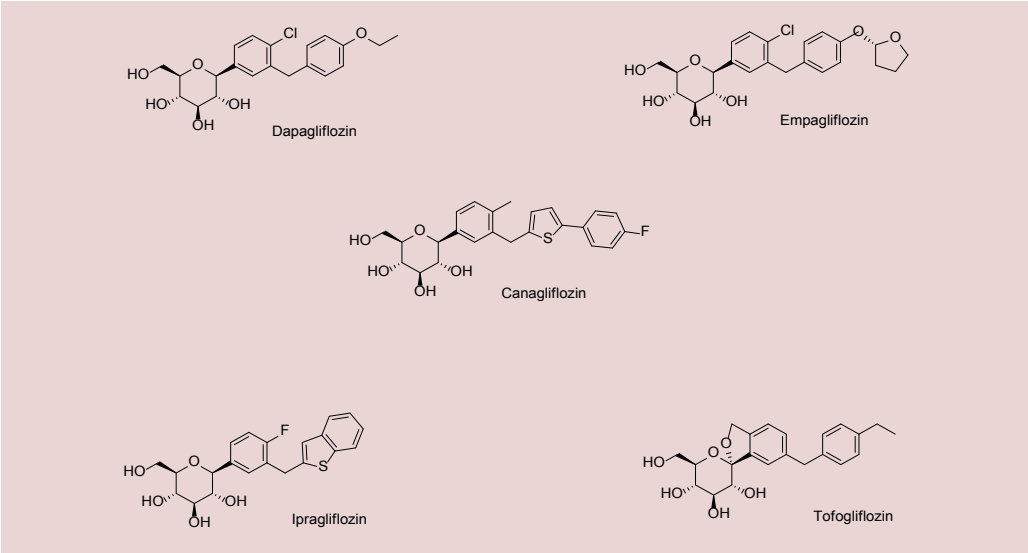


**Figure 4. New generation C-glycosidic antidiabetic drugs inspired by natural chalcone derivative structures.**

inhibition mechanism. First generation of synthetic analogs of phlorizin, were O-glycosides, which performed well as model inhibitors but failed clinical trials **(Figure 3)**.

The idea to replace O-glycosides by their C-linked analogs germinated slowly, for the lack of appropriate synthetic methods, which surfaced only at the end of the last century [44]. Relatively recent activation of C-glycosyl segment of carbohydrate chemistry afforded plethora of new, metabolically stable sugar conjugates and allowed to manufacture C-glycosyl analogs of phlorizin, which became successful new drugs [41,45] **(Figure 4)**.

## Conclusion

It can be concluded that low molecular weight FLAV constitute a collection of relatively high structural homogeneity, for obvious biogenetic reasons, which are not only interesting as multifunctional chemicals but have to be examined from the point of view of systems biology and their possible influence on human health. Their phenolic chemical character makes them particularly susceptible to action of certain type of enzymes (e.g. CYP450 and GTS) which results in introduction of hydroxyl groups and/or glycosylation. These changes can have profound influence on ADMET properties of FLAV as constituents of diet, which in turn decides on their pharmacodynamics and epigenetic effects which may be of medical interest. Majority of natural FLAV O-glycosides, which seem to be better suited for physicochemical properties tune up by various ways of chemical derivatization than their aglycones are not metabolically stable enough to undergo pharmacological and clinical tests of biological activity. C-Glyosidic compounds on the other hand can be considered particularly useful as both: model structures for virtual screening (e.g. for target affinities as well as for protein–protein interaction effects) as well as for new chemical entity synthesis.

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### Conflict of interest

Author declares no conflict of interest concerning this article.

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