Outcomes of Flavonoid-ABC-transporter Interactions

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Abstract
Flavonoids are common compounds found in plants and in herbal nourishments and medicines. These phytochemicals have many different functions in the plant kingdom. Besides, they may apply a wide variety of useful effects on human health in a broad range of disease states. The ATP-binding cassette (ABC) transporter superfamily comprise membrane-bounded proteins which are involved in the transport of a large assortment of substrates such as cholesterol, proteins, lipids, drugs, toxins and etc. ABC-transporter individuals are identified and grouped into seven subfamilies (ABC-A to ABC-G). Among these, three members are linked with multidrug resistance (MDR): P-glycoprotein (P-gp/ABCB1), the MDR-associated protein-1 (MRP1/ABCC1), and the breast cancer resistance protein (BCRP/ABCG2). Flavonoids can influence on ABC-transporters by affecting their ATPase function, which can be suppressed or stimulated depending on the type of these compounds. The purpose of this review is to provide evaluation of the data on the modulatory effect of flavonoids on P-gp, MRP1 and BCRP transporters particularly.

Keywords: flavonoids, ABC-transporters, multidrug resistance, drug efflux, SAR analysis.

Abbreviations:
ABC ATP-binding cassette
MDR Multidrug resistance
P-gp P-glycoprotein
MRP-1 MDR-associated protein-1
BCRP Breast cancer resistance protein
SAR Structure activity relationship
NBD Nucleotide-binding domains
qPCR quantitative polymerase chain reaction
ADR Adverse drug reaction

ფლავონოიდების და ABC- ტრანსპორტერების ურთიერთქმედების შედეგები

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რეზიუმე
ფლავონოიდები ფართოდ გავრცელებული ნაერთებია, რომლებიც გვხვდება მცენარეებში, მცენარეულ საკვებ პროდუქტებსა და მედიკამენტებში. ისინი წყალში ხსნადი პიგმენტებია და გააჩნიათ მრავალმხრივი ფუნქცია აქვთ. გარდა ამისა, მნიშვნელოვანია მათი სასრგებლო გავლენა ადამიანის ჯანმრთელობაზე; ფლავონოიდები გამოიყენებაიან მრავალი დაავადების სამკურნალოდ. ატფ დამაკავშირებელი კასეტის (ABC) ტრანსპორტერების (გადამზიდავები) სუპეროჯახი შედგება მემბრანის ინტეგრალური ცილებისგან, რომლებიც ჩართულია მრავალი სუბსტრატის, როგორიცაა ქოლესტერინი, პეპტიდები, მედიკამენტები, ტოქსინები და ა.შ. ტრანსპორტირებაში. ცნობილია ABC გადამზიდავების ინდივიდუალური წარმომადგენლები; ისინი კლასიფიცირებულია შვიდ ქვე-ოჯახში (ABC-A- დან ABC-G- მდე). მათ შორის, სამი ტრანსპორტერი ასოცირდება მრავლობითი წამლის რეზისტენტობასთან (MDR): პ - გლიკოპროტეინი (P-gp, ABCB1), MDR ასოცირებული ცილა -1 (MRP1, ABCC1) და მკერდის კიბოს - რეზისტენტობის ცილა (BCRP, ABCG2). ABC-გადამზიდავებზე შეიძლება გავლენა მოახდინონ ფლავონოიდებმა მათი ატფ-ის აქტივობაზე ზემოქმედების გზით. ფლავონოიდების ტიპის მიხედვით შესაძლებელია აქტივობის ინჰიბირება ან სტიმულირება. წარმოდგენილი სტატიის მიზანია ფლავონოიდების მოდულაციური ეფექტის მიმოხილვა P-gp, MRP1 და BCRP ტრანსპორტერებზე.

საკვანძო სიტყვები: ფლავონოიდები, ABC-ტრანსპორტერები (გადამზიდავები), მრავლობითი წამლის რეზისტენტობა, წამლის გამოდევნა, SAR ანალიზი.

შემოკლებები:
ABC - ატფ დამაკავშირებელი კასეტი
MDR - მრავლობითი წამლის რეზისტენტობა
P-gp - პ- გლიკოპროტეინი
MRP-1 - MDR ასოცირებული ცილა -1
BCRP - მკერდის კიბოს რეზისტენტობის ცილა
SAR - სტრუქტურა- აქტივობის დამოკიდებულება
NBD - ნუკლეოტიდის დამაკავშირებელ დომენი
qPCR - რაოდენობრივი პოლიმერაზული ჯაჭვური რეაქცია
ADR - წამლის არასასურველი რეაქცია

Introduction

Flavonoids. Flavonoids are the most common phenolic compounds found in human food such as vegetables, fruit and plant derivatives like wine and tea; they also contribute to the taste and color of these products. Furthermore, they are essential ingredients in a variety of herbal products, including herbal medicines and dietary supplements.(S. Zhang, Yang, & Morris, 2004).

A 15-carbon atom arrangement in a C6-C3-C6 configuration is the primary structure of flavonoids which consists of two aromatic rings, A and B, connected by a three-carbon atom bridge, typically in the form of a heterocyclic ring, C. The A-C ring structure is also known as a chromane ring (Fig. 1). The important flavonoid subgroups are formed by alteration in the substitution of the C ring, including the anthocyanidins (e.g., cyanidin), flavonols (e.g., quercetin, kaempferol), flavanols (e.g., catechin, epigallocatechin), flavones (e.g., apigenin, chrysin), isoflavones (e.g., genistein) and flavanones (e.g., naringenin, hesperetin). Different compounds in each subfamily are generated by substitutions of rings A and B (Pietta, 2000). Functionally, flavonoids are aqueous-soluble pigments which act varied role in the plants as well as growth, development, defense, UV protection, and so on (Buer, Imin, & Djordjevic, 2010). They are essential dietary components and may bring to play a wide spectrum of positive health impacts on human in a multitude of disease conditions including neurodegenerative diseases, cardiovascular disorders, cancers and osteoporosis (Morris & Zhang, 2006; Wasowski & Marder, 2012). Their activities also include anti-inflammatory, free-radical scavenging, antioxidant, antiviral, antimicrobial, anti-proliferative and pro-apoptotic effects (Buer et al., 2010; Wasowski & Marder, 2012).

ABC-transporters. In pharmacokinetic aspect of view, for absorption and being effective, drugs and their metabolites must pass through cell membranes, then be metabolized and excreted from the biological system. Cell membranes consist of many embedded proteins, including transport proteins, which have a major role in these paths. These proteins, belonging to the ABC super family, modify the pharmacokinetic of various drugs (Aszalos, 2008).

The ATP-binding cassette (ABC) transporter superfamily are membrane-embedded proteins which act on the transportation of variable substrates, such as lipids, cholesterol, bile salt, peptides, drugs, toxins, organic anions through extra- and intracellular bio membranes (Glavinas, Krajcsi, Cserepes, & Sarkadi, 2004; Hegedüs et al., 2012). The intracellular concentration of endo- and exogenous substrates is restricted by active efflux of these compounds via binding and hydrolysis of ATP. Around 50 human ABC-transporter proteins are identified and grouped into seven subfamilies (ABC-A to ABC-G); from the known transporters three are related with multidrug resistance (MDR): P-glycoprotein (P-gp, ABCB1), the MDR-associated protein-1 (MRP1, ABCC1), and the breast cancer resistance protein (BCRP, ABCG2)(Choudhuri & Klaassen, 2006; Robey et al., 2009; Staud & Pavek, 2005).

ABC-transporters not only limit the bioavailability of xenobiotics but also possibly interact with drugs and dietary substances, being understood about the interactions between flavonoids and ABC-transporters are necessary to consider potential food–drug and herbal product–drug interactions (Alvarez et al., 2010).

Modulation of ABC-transporters activity by flavonoids. Different mechanisms of interaction between ABC-transporters and flavonoids have been identified, including via an impact on the ATPase activity of ABC-transporters. In fact, flavonoids such as quercetin and genistein can hinder (Pulido et al., 2006) or other flavonoids like glabridin can stimulate the ATPase activity (Cao et al., 2007). Besides, another way of ABC-transporters inhibition is when flavonoids are transported by the ABC-transporters, so they compete with other substrates. Therefore, in this case, flavonoids might inhibit the transportation of other xenobiotics by ABC-transporters (Alvarez et al., 2010).

Effect of Flavonoids on activity of P-Glycoprotein. P-gp was first characterized in 1976 in Chinese hamster ovary cells (Juliano & Ling, 1976). Polarized cells such as colon, liver, kidney, jejunum, and adrenal gland with secretory function blood (Malik, Sharma, & Jain, 2017) and also in cells which act as the barrier for instance the blood-brain barrier (Ferreira, Pousinho, Fortuna, Falcão, & Alves, 2015) that physiologically preserve the body from xenobiotics, placental fetal barrier have been identified to have P-gp in their membranes. P-gp has a broad spectrum of substrates that differ not only in structure and size but as well in various chemical properties (Chambers et al., 2019). Many flavonoids (silymarin, genistein, epicatechingallate, catechingallate) have capability for directly attachment to the binding site of the P-gp substrate (Malik et al., 2017). Silibinin and semi-synthetic products of this compound illustrated

regulation capacity of P-gp and ability to inhibit its efflux (Džubák et al., 2006). Furthermore, silymarin was described that is able to attach to either ATP binding sites of P-gp and substrate in vitro (Shuzhong Zhang & Morris, 2003). However, owing to the fact that, it is a mix of several components, scientifically this assessment is erroneous. Kaempferol, quercetin, rutin, chrysin, naringeninand genistein, directly interact with the ATP-binding site. The mechanism of inhibition of epicatechin is stated as a heterotropic allosteric initiation. Opposite, flavanone and isoflavones glycosides had no effect on inhibition of P-gp. Some of these bioflavonoids, i.e. quercetin, biochanine A and epigallocatechin gallate, if applied to resistant cells had a biphasic effect: in low concentrations (about 10μM), they acted as stimulator of the transport by P-gp pump; but, in larger doses (50-100μM), these compounds were distinctive inhibitors. This dose-related pattern of P-gp inhibition has been described for some bioflavonoids such as naringin, fisetin (Ferreira et al., 2015).

SAR (structure activity relationship) studies were performed for 40 dietary flavonoids for their P-gp inhibitory action screening. In one concentration (10μM) assessment, number of bioflavonoids entirely failed and others illustrated insignificant potential in inhibition. Silybin, myricetin, naringin, tamarixetin, pelargonidin and epicatechin 3-O-gallate displayed medium inhibitory action, and quercetin (IC50= 7μM), rutin (IC50= 8μM) and theaflavin (IC50= 20μM) showed high inhibitory potency. Either, rutin and quercetin were capable to maintain the P-gp-based resistance at 10μM concentration (Mohana et al., 2016). Baicalein also acted in similar way, an isolated flavonoid e.g. from Scutellaria radix(J. Li et al., 2018). In addition, quercetin exhibited prevention effect on doxorubicin resistance resulted by decreasing P-gp expression (Laberge, Karwatsky, Lincoln, Leimanis, & Georges, 2007). Correspondingly, kaempferol, naringenin and icaritin, downregulated P-gp overexpression at the transcriptional level. The P-gp is ABC efflux transporter that was first reported with clinical significance, and the animal tests with bioflavonoids as inhibitors of P-gp have been done. It was revealed that the pre-treatment with quercetin, silymarin, morin,or has better results rather than co-administration of the drug with these compounds (Chambers et al., 2019; Choi & Li, 2005; Sun, Chen, Qu, Wu, & Si, 2013).

Regulation of MRP-1 activity by flavonoids.

MRP1 was discovered first as a reason of multidrug resistance in pulmonary carcinoma cells in 1992 (S. Cole et al., 1992) and then in other polarized cells (e.g. skeletal muscles, cardiac, skin and colon) (Lorendeau et al., 2017). Currently, it is evident that MRP1 serves a wider function than only moderating the ATP-dependent drugs efflux from cells. In the structure, it is similar to P-gp and comprises by 12 trans-membrane domains, many different loops, and two cytosolic nucleotide-binding domains (NBD). Physiologically the major action of this transporter is being capable to efflux either lipophilic or lipophobic xenobiotics plus the transportation of oxidized and reduced form of glutathione and its conjugates(S. P. Cole, 2014). In humans MRP1 is located in the basolateral membrane of the choroid plexus, liver, in cancer tissues, at the blood brain barrier and the blood cerebrospinal fluid barrier (Borst, Evers, Kool, & Wijnholds, 2000).

A rise in accumulation of doxorubicin in U-2 osteosarcoma cells transfected with MRP1, was shown for flavonostilbenes: alopecurone A, B, and D, which were obtained from Sophoraalopecuroides. At the non-toxic concentration (20μM), on these cells, these flavonoids reduced the doxorubicin IC50 by 12, 5, and 8 times, respectively. In accordance with the performed qPCR measurement, the MRP1 overexpression was remarkably influenced by the flavonostilbenes (Ni, Yang, Wan, Xia, & Kong, 2014). Though, other examined flavonostilbenes: lehmannin, alopecurone F, liquiritin, sophoraflavanone G and luteolin did not demonstrate this potential. Other flavonoids, such as biochanin A, kaempferol, quercetin, apigenin, genistein, naringenin, silymarin, phloretin, myricetin, morin, chrysin, and chalcone inhibited the MRP-1-mediated transportation(Abdallah, Al-Abd, El-Dine, & El-Halawany, 2015; Lorendeau et al., 2017).

The higher capacity has been found in flavonoid dimers such as apigenol dimer. The action mechanisms involve the regulation of ATPase activity shown by dehydrosilybin and to compete with substrate transportation illustrated by alvocidib (Lorendeau et al., 2017). 8-prenylnaringenin also inhibited the MRP-1 activity (Abdallah et al., 2015). Similar to suppression of P-gp, quercetin inhibited MRP1 overexpression and reversed the resistance phenotype in stomach cancer cells (Hyun, Moon, & Cho, 2018). Bioflavonoid kaempferol also down regulated the expression of these two transport proteins in pro-myelocytic leukemia cells(Moradzadeh et al., 2018) and icaritin - in osteosarcoma cells(Zhen-Dong, Rui-Zhi, Yuan-Zheng, Ling-Yi, & Lei, 2018). At last, MRP1 overexpression and activity was as well inhibited

by Apigenin 8-C-glucoside in colorectal cancer cells(Bhardwaj et al., 2018).

Modulatory effects flavonoids on BCRP activity. In 1998 BCRP was cloned from a multidrug resistant breast cancer cell line(Doyle et al., 1998) and then has been additionally detected in the intestine, central nervous system, brain endothelium and prostate. BCRP is not similar to the other transport proteins it contains only one nucleotide-binding domain and one trans-membrane domain. Although the structure of breast cancer resistance protein has not been resolved so far; and it is assumed to be dimerized. BCRP acts for the first barrier for drug absorption in the intestine, blood–brain barrier, the maternal–fetus barrier and other body barriers. Physiologically its action is associated with the avoidence of distribution of xenobiotics. At the moment, many regulators of BCRP transporter with a phenolic structure have been issued in reference to data obtained from BCRP over expressed cell cultures: quercetin; fisetin; genistein; kaempferol; apigenin; luteolin; biochanin A; 5,7-dihydroxyflavone; daidzeol; luteolin 4'-methyl ether; hesperetin; laricitrin; myricetol; naringenin; chrysoeriol; phloretin; silybin; tamarixetin. Among all of these substances, the following flavonoids are the most favourable modulators: kaempferol, apigenol; chrysoeriol; luteolin 4'-methyl ether and tamarixetin which have an IC50 value below 0.1μM similarly as the reference compound, Kol43 (selective BCRP inhibitor, diketopiperazine structure) (Peña-Solórzano, Stark, König, Sierra, & Ochoa-Puentes, 2017).
The idea of so-called hybrid compounds is a potential moderately new direction in the area of bioactive compounds. These hybrids are made up of two or more moieties bound in a single structure using different methods. These hybrids show less sensitivity to cancer cell resistance development (Kucuksayan & Ozben, 2017). First, experiments were achieved with an antioxidant and photo-protectant structure based on octylmethoxycinnamate, trans-resveratrol and avobenzone subunits (Reis, Correa, Chung, & Dos Santos, 2014). Then, flavonoids quercetin andgenistein, were employed for the synthesis of a library of hybrid molecules, either genistein or quercetin on human prostatic carcinoma, showed a higher anti-proliferative potential than the parent compounds. (Chen et al., 2015).
On the Bases of diverse SAR studies, the ideal structure of flavonoids with more potent inhibitory effect on these transporters is defined (Fig. 2). Modulators of P-gp transporter with flavonoid structure-based should be lipophilic molecules with a planar structure; 2,3-unsaturated in ring C, and 5,3-hydroxylated and together with weak positive charge at physiological pH; (Ferreira et al., 2015; Mohana et al., 2016). The whole number of hydroxyl groups have an important impact on inhibition, for instance, structures with three hydroxyl groups show a high inhibitory ability while four-hydroxylated molecules have a soft impact, and pentahydroxylated structures promote P-gp action(Ferreira et al., 2015; Sheu, Liou, Kao, Lin, & Ho, 2010). According to SAR analysis, the most notable MRP-1 inhibitors could involve resveratrol and lavandulyl moieties (Ni et al., 2014). For the interaction of Nucleotide-binding domains with flavonoids, C-5- and 7-hydroxy groups on the A-ring as well as 2,3-double bond in ring C are critical. Furthermore, the position and number of another methoxy and hydroxy functional groups modify the suppressing activity remarkably(Lorendeau et al., 2017). For inhibition of the BCRP transporter, the presence of a 2,3-double bond in ring C, binding of ring B to the location C-2, a hydroxyl group at the location C-5, an absence of the hydroxyl group at location C-3 although it is advantageous that methoxy group being present, and a lipophilic functional group at some of the locations C-6, C-7, C-8, or C-4′ are essential(Peña-Solórzano et al., 2017).

Flavonoids modify the expression of ABC-transporters. Numerous explorations scoped with the inhibitory impact of secondary metabolites on transporter action, though many phytochemicals modify the expression of related genes; in particular, polyphenolic compounds (Tinoush, Shirdel, & Wink, 2020) which the results of some of these studies are discussed here. Ampelopsin downregulated P-gp in K562/ADR cell line and it has synergistic effect with adverse drug reaction (ADR). Therefore, ADR cytotoxicity and accumulations in the cells are increased(Ye, Zheng, & Liu, 2009). Baicalein increased in MDR1 expression in LS174T cells (Yue Li, Wang, Yao, & Li, 2010). Epicatechingallate caused downregulation of the expression of MDR1 and P-gp in Bel-7404/DOX cells (Liang et al., 2010). Besides, in MCF-7Tam cell lines induced a decrease in P-gp and BCRP expression (Farabegoli, Papi, Bartolini, Ostan, & Orlandi, 2010).

Conclusions. Flavonoids are a ubiquitous group of polyphenolic compounds which are found in natural products. Them and their metabolites are believed to show modulatory effects on membrane-bound transporters activity and expres-

sion. Due to the fact that consumption of flavonoid-containing products are growing; therefore, the investigation of food-drug and herbal product-drug interactions is becoming more notable.
In this review article, several studies were presented which focused on pharmacological activity of numerous phytochemicals counting flavonoids. In particular, their modulatory impacts on three MDR-associated ABC-transporters which are P-gp, MDR1 and BCRP were examined.
Different mechanisms for the interaction of flavonoids with ABC-transporters have been detailed. Flavonoids can influence on ATPase activity of these transporters which may show inhibitory or stimulatory impact. Furthermore, flavonoids may be transported by ABC proteins as their substrate and this may be another possible flavonoid-modulatory mechanism which causes a competitive inhibition between flavonoids and their metabolites with other xenobiotics.
In conclusion, flavonoids are probable candidates for interferences among drugs, foods and herbal products which should be considered in MDR studies and ligand-based attitude for drug design.

Figure 1. Molecular structure of flavonoids(Y. Li & Paxton, 2013).

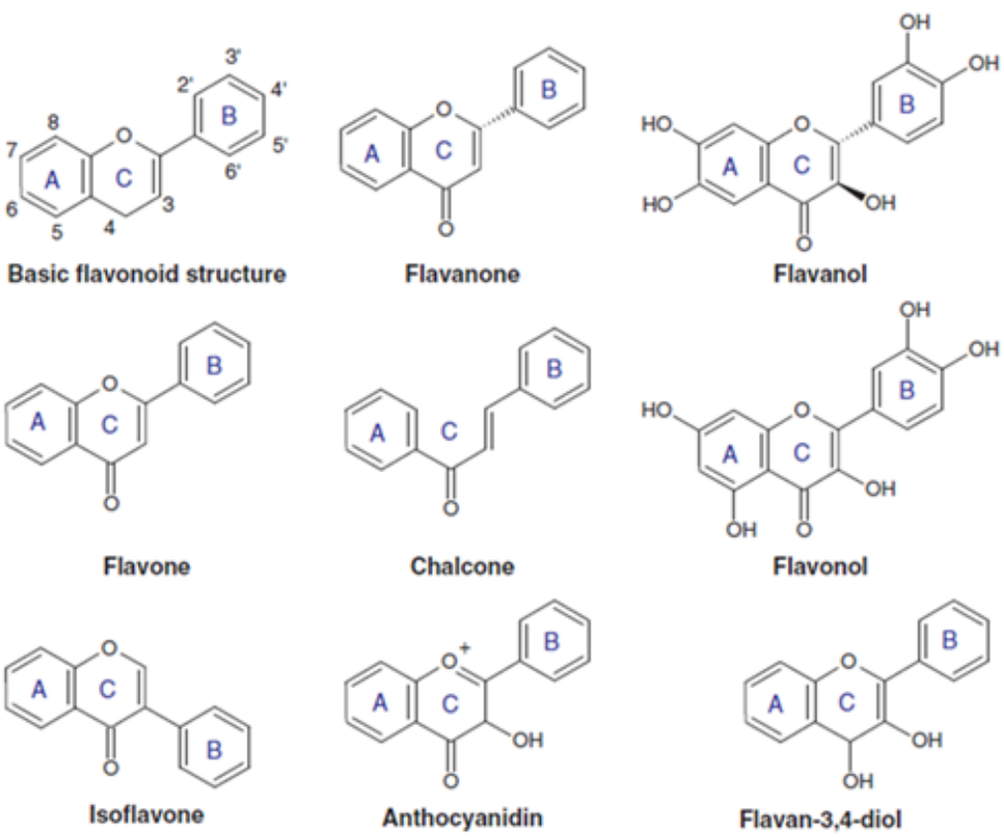
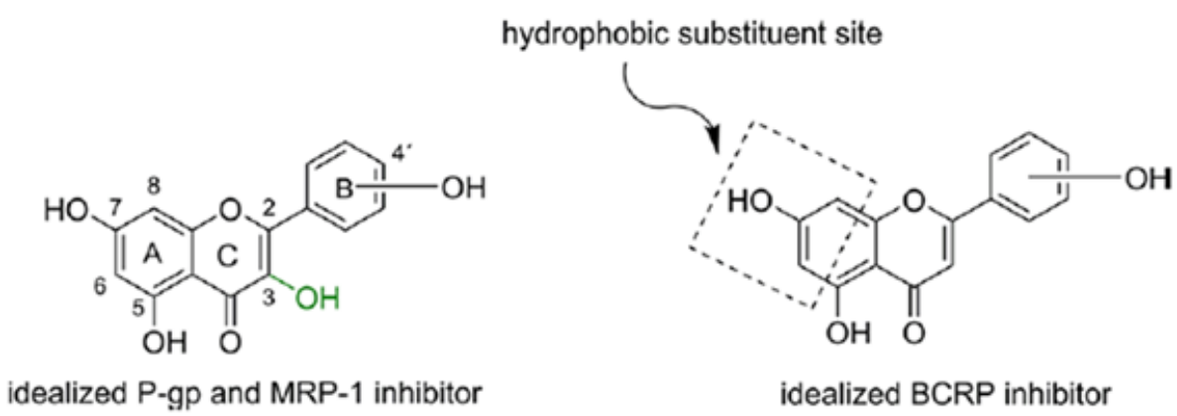


Figure 2. Ideal structures of MDR inhibitors(Chambers et al., 2019).



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