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Review Article

Modulation of membrane transporter expression and activity by mangiferin, epigallocatechin-3-gallate (EGCG), quercetin, and kaempferol: A review

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Abstract

Membrane transporters are one of the important factors in drug pharmacokinetics. These proteins mediate drug transport in and out of cells; efflux transporters export the drug from inside the cell, while influx transporters facilitate the entry of it into the cell. Thus, the presence of these membrane proteins influences drug levels in cells, which then determines the drug efficacy and safety profile. Numerous studies have demonstrated that various exogenous compounds can modulate the activity and/or expression of membrane transporters, including bioactive molecules. Flavonoids are secondary plant metabolites that are very abundant and widely used in diets, supplement products, and traditional medicine. Apart from their medical benefits, flavonoids have been reported to interact with membrane transporters involved in drug absorption and drug resistance. These interactions can be beneficial in multidrug resistance conditions or awareness of drug toxicity. This article collects studies that have been conducted on four widely consumed plant-derived compounds: mangiferin, epigallocatechin-3-gallate (EGCG), quercetin, and kaempferol, and their effects on membrane transporters. The effects can be a consideration when administering these flavonoids together with medication.

Keywords: Drug interaction, Efflux, Flavonoids, Influx, Membrane transporter, Multidrug resistance

Review: Modulasi ekspresi dan aktivitas transporter membran oleh mangiferin, epigallocatechin-3-gallate (EGCG), kuersetin, dan kaempferol

Abstrak

Transporter membran menjadi salah satu faktor penting dalam farmakokinetik obat. Protein ini memediasi transpor obat masuk dan keluar sel; transporter efluks mengeluarkan obat dari dalam sel, sementara transporter influks memfasilitasi masuknya obat ke dalam sel. Jadi, adanya protein membran ini memengaruhi kadar obat di dalam sel, yang kemudian menjadi penentu profil efikasi dan keamanan obat tersebut. Banyak penelitian telah menunjukkan berbagai senyawa eksogen yang dapat memodulasi aktivitas ataupun ekspresi transporter membran, termasuk molekul bioaktif. Flavonoid merupakan metabolit sekunder tanaman yang sangat melimpah dan dikonsumsi secara luas dalam diet, produk suplemen, dan pengobatan tradisional. Di samping manfaat medisnya, flavonoid dilaporkan dapat berinteraksi dengan transporter membran yang terlibat dalam absorpsi maupun resistensi obat. Interaksi-interaksi tersebut dapat menjadi manfaat dalam kondisi resistensi obat ataupun kewaspadaan terhadap toksisitas obat. Artikel ini mengumpulkan studi-studi yang telah dilakukan terhadap empat senyawa turunan tumbuhan yang digunakan secara luas: mangiferin, epigallocatechin-3-gallate (EGCG), kuersetin, serta kaempferol, dan efeknya pada transporter membran. Pengaruh yang ditimbulkan dapat menjadi pertimbangan dalam pemberian flavonoid tersebut bersamaan dengan obat.

Kata Kunci: Interaksi obat, Efluks, Flavonoid, Influks, Transporter membran, Resistensi obat

1. Introduction

Membrane transporters are key proteins that are involved in regulating the levels of compounds in cells, with the main function being to protect cells and organs from compounds that are toxic to these cells and organs (efflux transporters) or to absorb compounds into cells to be metabolized or excreted (influx transporters). Membrane transporters are important determinant in the pharmacokinetics of drugs, especially in the metabolism and elimination stages, which can help determine the therapeutic efficacy and safety of the drug.[1]

The activity and/or expression of membrane transporters can be modulated by xenobiotic compounds, including drugs, natural-derived compounds; they can be inhibited or enhanced. Bioactive compounds, especially from plants, are widely used in traditional medicine because they have a variety of biological as well as pharmacological activities. In addition, about 30% of currently available drugs also contain active compounds of plant origin. However, their use can lead to interactions with other drugs or compounds. These interactions may appear as a result of the modulation of membrane transporters, the modulation of Cytochrome P450 (CYP450) isoenzymes, multidrug transporters like P-glycoprotein (P-gp), or a combination of the two.[2]

There are many natural compounds that have been shown to inhibit the function and modulate the expression of transporters. For example, P-gp transporters are affected by plants secondary metabolite such as St. John's wort, capsaicin (chili), curcuminoids from turmeric or Javanese turmeric, kaempferol, quercetin, piperine from pepper, mangiferin from mangoes, and others.[2] Most of the phytochemicals that can modulate the P-gp transporter are from the curcuminoid and flavonoid groups.[3] Many reports showed that flavonoids inhibit ABC transporters that contribute to the development of multidrug resistance (MDR).[4] In addition to P-gp transporters, influx transporters can also be modulated by bioactive compounds, such as Epigallocatechin-3-gallate (EGCG), the main catechin of green tea (*Camellia sinensis*), which is also reported to reduce the efflux activity of P-gp transporters.[5,6]

Potential modulation of transporters by natural substances could lead to alterations in the pharmacokinetic profile of drugs or other compounds that are substrates of these transporters. This is important because most of the drugs are administered orally. Hence, the bioavailability of these compounds can already be affected by drug transport and metabolism, particularly in the intestine.[7] If the activity or expression of an influx transporter is decreased, there will be an obstacle to the entry of the drug into the target cells to be metabolized or exert its therapeutic effect, thereby increasing excessive blood concentrations that can lead to undesirable side effects. The decreased activity or expression of the efflux transporter protein may contribute to accumulation of substrate compounds, which if the compounds are toxic, will pose a danger to the cell. Conversely, if the efflux transporter increases in activity or expression, it can cause a decrease in the level of the compound in the cell because the compound is continuously pumped out by the efflux transporter. However, it turns out that this regulation of efflux transporters is needed to treat MDR conditions, since this phenomenon can be caused by several mechanisms including enhanced drug efflux from cells via transporters.[8] Therefore, it is crucial to understand the effects of various compounds on membrane transporters to be taken into consideration when administering certain drugs. In this paper, we review several bioactive compounds derived from plants, namely mangiferin, epigallocatechin-3-gallate, quercetin, and kaempferol, and their effects on transporters. These are several compounds contained in plants that are easily found and often consumed as daily diet or herbal supplement. By knowing how these compounds affect drug transporters, their use in conjunction with drugs either as concomitant or the consumption of food or health supplement containing these compounds can be considered.

2. Methods

To write this review, we searched electronic databases and we restricted from 2012–now. The keywords used were: membrane transporter, the expression and activity of membrane transporters, biological and pharmacological activity of plant extract and bioactive compound. Searches were conducted between 20 February–30 March 2022. Inclusion criteria were all papers in English and Indonesia about natural compound in relation to its effects on activity and expression of membrane transporter, while the exclusion criteria were articles that are not related to the topic.

3. Results and Discussion

3.1. Membrane Transporter

Membrane transporter, a protein that is embedded in biological membranes in all organisms,[9] facilitates the translocation of ions and small molecules across the membrane. It is located both at the plasma membrane and membrane of intracellular compartments such as lysosomes, mitochondria, and other vesicles.[10] Thus, these proteins are involved in the movement of nutrients, waste, toxins, and xenobiotics (including drugs and bioactive compounds) in and out of cells. In the human genome, there are approximately 30% or 2,000 genes encoded for membrane transporters or other proteins related to the transporter.[1,11]

One of the mechanisms of drug transport across the membrane is facilitated by membrane transporters; efflux transporters to remove or export drugs from inside to outside the cell, and influx transporters to absorb (uptake) drugs into the cell. In general, efflux transporters are consisting of two types: permeability-glycoprotein (P-gp) and multidrug resistance protein (MRP). These efflux transporters facilitate active transport and thus require energy from ATP hydrolysis. Influx transporters are divided into several types, namely organic anion transporting polypeptide (OATP), organic anion transporter (OAT), and organic cation transporter (OCT).[12] Each gene encoding transporter protein may depend on different transcription factors to activate the transcription of the gene to produce a different transporter.

These proteins, that can be found in the plasma membrane in various organs, facilitate efficient cellular metabolism, assist in nutrient sensing, and are also linked to various diseases such as obesity and cancer.[13] Several membrane transporters also serve a role in increasing the resistance of tumor cells to drugs used in anticancer therapy.[10] In the MDR phenomenon, there are two underlying mechanisms: 1) insufficient amount of drug in the cancer cells and 2) intracellular changes that interfere with the drug's ability to kill cancer cells, such as inhibition of apoptosis, increased repair of damaged deoxyribonucleic acid (DNA), and changes in drug metabolism. This accumulation of anticancer drugs might be controlled by membrane transporters. In addition to drug resistance in the therapy of anticancer, these membrane proteins also play a role in the development of resistance to other drugs, such as antiviral and anticonvulsant agents.[9]

Over 400 membrane transporters identified in the human genome are categorized into two superfamilies: the ATP-binding cassette (ABC) family and solute carrier (SLC) family.[11,14] In general, membrane proteins are divided into two types, which are influx and efflux transporters. Efflux transporters facilitate the expulsion of compounds from inside to outside the cell. The efflux transporter includes proteins belonging to the ABC superfamily. This is one of the biggest families coded in the human genome.[15] It is known that this type of transporter is found in all organisms, from bacteria to humans. ABC transporters embedded in the cell membrane and its ATP binding site is known as 'ABC cassette'. The ABC superfamily consists of 49 genes, each containing one or two fixed ABC regions. The ABC catalytic core region of this protein binds and hydrolyzes ATP, and uses energy for uphill transport, expelling substrates across the membrane. In eukaryotes, most of this transporter transport compounds from the cytoplasm to extracellular or intracellular compartments such as endoplasmic reticulum, mitochondria,

and peroxisomes. Meanwhile, in prokaryotes, ABC transporters primaryly facilitated the import of essential compounds that cannot be transported by passive diffusion (e.g. sugars, vitamins, metals, etc.).[16] Basically, efflux transporters function as cell defense from toxic foreign substances or compounds by preventing them from entering the cell. In other cases, if there is a compound that is not recognized by this transporter and enters the cell, the detoxification enzymes will modify it into a more hydrophilic form to be released by the efflux transporter to the outside of the cell.

One of the most expressed efflux transporters is P-gp transporters, making it the most studied one. P-gp belongs to ABC transporter subfamily B1 (ABCB1/ MDR1 gene).[17] It is found in multiple tissues throughout the body, with the highest expressed in organs that play a role in handling chemical compounds such as the liver, kidneys, and intestines. P-gp transporters are active transporters; it uses the energy from ATP hydrolysis, with the physiological function of cell and organ protection. P-gp plays an important role as it mediate various drugs or exogenous substances to be transported across the membrane. Some P-gp substrates include doxorubicin, vinblastine, docetaxel, gefitinib, calcein AM, dexamethasone, morphine, erythromycin, lovastatin, ivermectin, verapamil, digoxin, cyclosporine A, and many others.[3] As it can be found in multiple tissues and organs, the activity of this protein is highly crucial for the metabolism of numeorous drugs that are its substrates.[18] Drug absorption can be affected by the co-administration of P-gp inducers or inhibitors; inhibitors may enhance the bioavailability of drugs while inducers may decrease it.[4]

P-gp transporters are associated with cell resistance to certain drugs, as they are one of the main mediators in drug-drug or drug-herbal interactions.[19] Resistance to cancer chemotherapy is the most common case of drug resistance, and it is reported that P-gp is accountable for the low accumulation of anticancer drugs,[20] as it increase drug efflux of chemotherapeutics from cancer cells. The activity and expression of these transporters are said to be affected by various chemical factors, such as hormones, vitamins, drugs, cytokines, carcinogens, and food. Besides P-gp, efflux transporters also consist of multidrug resistance protein (MRP, encoded by the ABCC gene) transporters and breast cancer resistance protein (BCRP, encoded by the ABCG2 gene).

Influx transporters, also known as uptake transporters, act in nutrient uptake into the cell. Not only that, these proteins are important in the intracellular movement of compounds, including drugs or natural compounds, where they are brought into contact with metabolizing enzymes for elimination or to elicit biological or therapeutic effects from the drug compound.[1] Most of the influx transporters are facilitated transporter or secondary active transporter whose action depends on the electrochemical gradient or ion gradient generated by ATP-dependent pumps. The influx transporters belong to the SLC superfamily which consists of at least 52 genes encoding about 395 different transporters. SLC substrates include ionic and non-ionic compounds as well as various xenobiotics, including drugs.[16]

3.2. Modulation of Membrane Transporters by Flavonoid

The most extensively studied membrane transporter is the ABC transporter, because it is closely related to MDR events. Among those, the ABC transporters with the greatest pharmacological significance are located in the apical membrane of cells. These transporters include P-gp/ABCB1, MRP2/ABCC2, and BCRP/ABCG2. The interaction of ABC transporters with flavonoids is an important to pay attention to since the drug absorption, pharmacokinetics, biotransformation, and tissue distribution are factors that determine drug effects.[21]

Studies suggested that flavonoids regulate ABC transporters by several mechanisms. For P-gp expression, it is usually mediated by multiple pathways, including CYP3A4, nuclear factor kappa B (NF-

κB), the mitogen-activated protein kinase (MAPK) pathway, phosphoinositide 3-kinase (PI3K), and cylooxygenases- 2 (COX-2). For MDR, it is suggested that MAPK/ERK and NF-κB are the more reliable mechanism.[22] ABC transporters activity can be inhibited by flavonoids by modulating its ATPase activity. Flavonoids also act as transporters substrate, then causing competitive inhibition towards other compounds. Flavonoids are recognized as substrates of all the most pharmacologically relevant ABC transporters.[21] Therefore, flavonoids can affect these proteins. In addition, several other studies also show the effect of flavonoids on other membrane transporters, including influx transporters. We discuss below several studies on the effects of mangiferin, EGCG, quercetin, and kaempferol on membrane transporters.

3.3. Mangiferin

Mangiferin (Figure 1A) is a polyphenolic xanthone that is commonly found in the Anacardiaceae family and is the most known compound of the mango plant (*Mangifera indica*). Mangiferin in mangoes can be found in different parts of the plant, including leaves, kernels, fruit peels, and bark.[23] Mangiferin also contained in Phaleria macrocarpa plant. Mangiferin has been thoroughly investigated for its biological and pharmacological activities, both in vitro and in vivo. In addition, the effect of mangiferin on membrane transporters was also investigated.

In vitro studies performed by Chieli et al. (2009) examined the effect of mangiferin compounds on the activity of the P-gp transporter in Human Kidney 2 (HK-2) cells expressed in renal tubules. Results showed that the administration of mangiferin caused a dose-dependent increase in the intracellular fluorescence of rhodamine-123 (Rh-123), a substrate of P-gp.[19] Under normal conditions, Rh-123 will be pumped out by P-gp so that its intracellular accumulation will be low. An increase in the intracellular fluorescence of

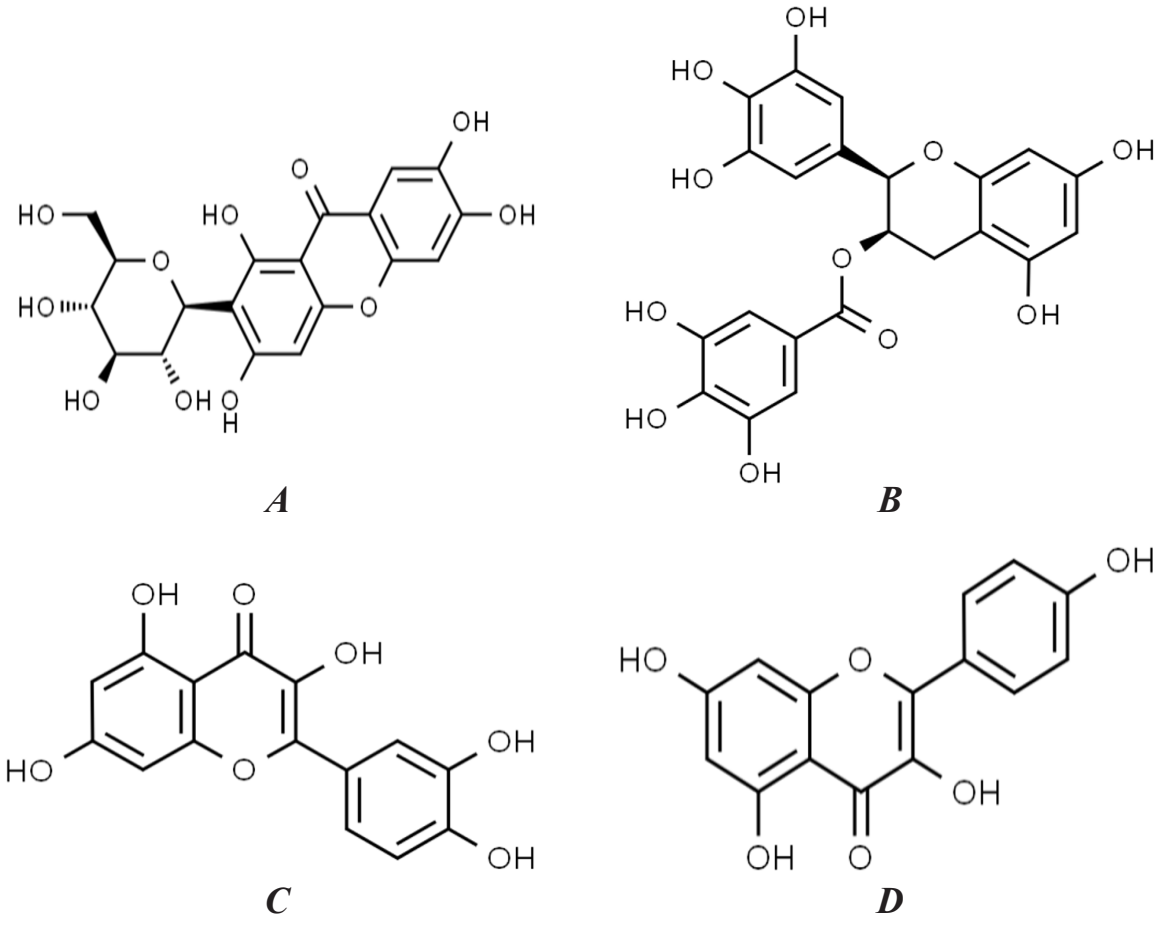

Figure 1. Chemical structure of (A) mangiferin ($C_{19}H_{18}O_{11}$); (B) EGCG ($C_{22}H_{18}O_{11}$); (C) quercetin ($C_{15}H_{10}O_7$); (D) kaempferol ($C_{15}H_{10}O_6$). Picture is adapted from Chemspider, Royal Society of Chemistry (CSID 4444966, 58575, 12269344, 4444395 respectively)

Rh-123 indicates an increase in the amount of the compound entering the cell, which means that there is an inhibition of P-gp activity in exporting the compound out of the cell (Figure 2).

In vivo, mangiferin is metabolized into its aglycone form, norathyriol (1,3,6,7-tetrahydroxyxanthone). Therefore, the ability of this aglycone metabolite to affect the P-gp transporter was also investigated. In line with mangiferin, norathyriol administration also demonstrated a dose-dependent rise in intracellular Rh-123 fluorescence. However, the efficacy of these two compounds showed different results. Norathyriol at a low concentration (5 µM) was already able to increase fluorescence significantly, while mangiferin only started to show a significant increase at a concentration of 10 µM. The dose-dependent increase resulting from mangiferin administration was also not very significant compared to norathyriol. At the highest dose tested, mangiferin increased fluorescence by only 72% compared to the control, while norathyriol increased fluorescence up to 250% compared to the control. Norathyriol has a more significant effect on the inhibition of the P-gp transporter when compared to mangiferin itself. This is in line with several investigations on the biological and pharmacological activities of phytochemicals which concluded that the aglycone of a compound is usually more active than its parent glycoside. In the case of mangiferin with its aglycone norathyriol, what has been proven in previous studies is that mangiferin is less active in inhibiting peroxisome proliferator-activated receptors (PPARs) transactivation, while about multidrug transporters, many phenolic compounds have been shown to interact more effectively when the compound is in its aglycone form.[24,25,26] Thus, it is indicated that norathyriol, a metabolite of mangiferin, plays more of a role in interactions with P-gp compared to mangiferin.[19]

Further in vitro studies conducted by Chieli et al. (2010) reported that mangiferin which is the most abundant polyphenol in M. indica also has an effect on ATP-Binding Casette subfamily B member 1 (ABCB1)/P-gp expression.[2] If in the previous explanation,

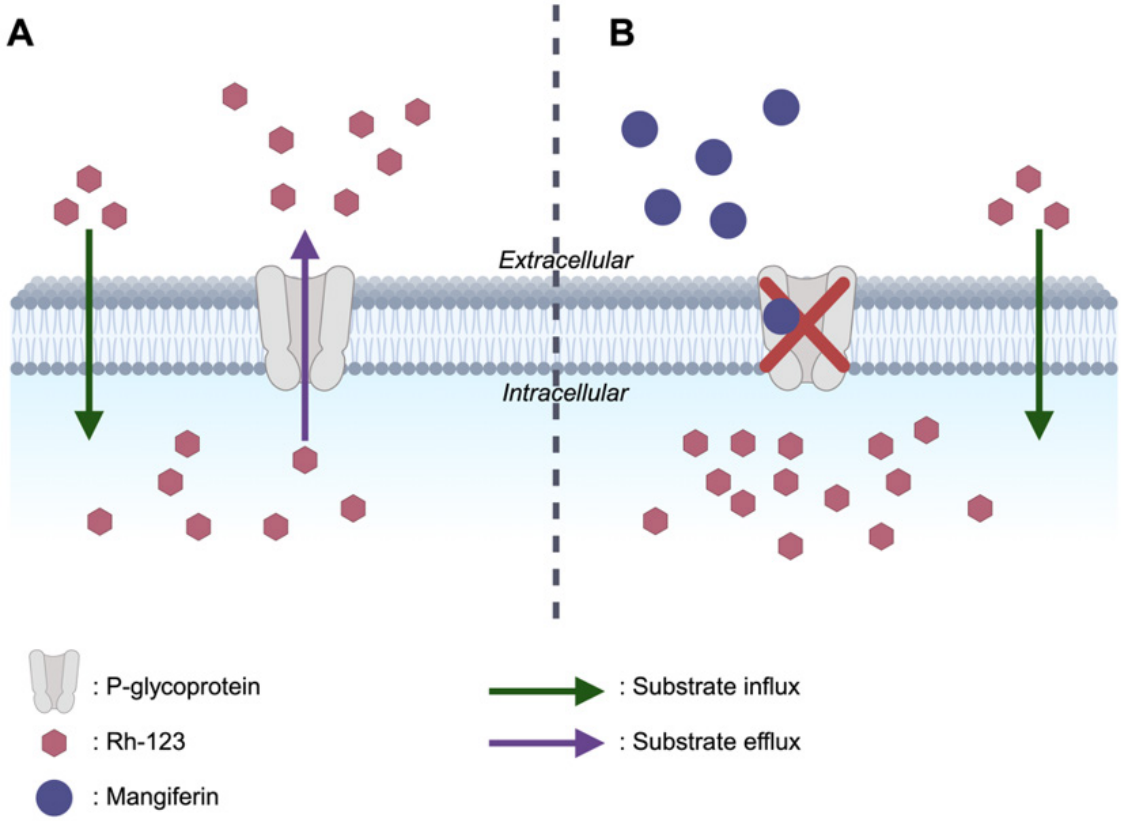

Figure 2. Inhibition of P-glycoprotein (P-gp) activity by mangiferin: (A) P-gp substrate Rh-123 pumped out of the cell cytoplasm by P-gp; (B) the efflux activity of P-gp is inhibited by the presence of mangiferin molecules. Illustration is created with BioRender.com

Table 1. Overview of studies of the effects of mangiferin and its derivative on P-gp transporter

Compound	Membrane Transporter	Effects	Reference
Mangiferin	P-gp	Inhibition of its activity in HK-2 cells	(19)
		Upregulation of P-gp protein and ABCB1 mRNA expression in HK-2 cells	(2)
Norathyriol	P-gp	Inhibition of its activity; greater effect than Mangiferin	(19)

it was said that mangiferin was capable of inhibiting the activity of the P-gp transporter, its effect on P-gp expression showed the opposite result. Mangiferin was able to upregulate P-gp expression by increasing the transporter protein along with ABCB1 messenger ribonucleic acid (mRNA). A notable increase in the levels of P-gp and ABCB1 amplicons occurred at mangiferin concentrations of 50 and 200 μM.

This increase in gene expression can be due to two things; an increase in the transcription rate or a decrease in mRNA turnover. The increased expression of ABCB1 by mangiferin is thought to be resulted from transcriptional upregulation, as reported by a study by Chieli et al. (2010) which showed that mangiferin administration increased the amount of ABCB1 mRNA, while in the group given mangiferin together with 1-dribofuranosylbenzimidazole (DRB) which is a transcriptional inhibitor showed inhibition of this increase.[2]

Mangiferin's ability to produce anti-inflammatory effects, antioxidants, and other benefits is thought to be derived from its activity in inhibiting NF-κB, which is a transcription factor involved in regulating P-gp expression. Therefore, the expression of P-gp transporters should be suppressed by mangiferin. This contradicts the study described above, that mangiferin upregulates P-gp expression. It indicates that the phenomenon of P-gp upregulation by mangiferin is mediated by factors not related to NF-κB. Besides the NF-κB pathway, there are other signaling pathways involved in the expression or activity of ABC transporters. For example, in some cases, upregulation of ABCB1 by phytochemical compounds occurs through mechanisms related to CYP expression by upregulation of nuclear receptors such as pregnane X receptor (PXR).[27] However, since mangiferin is reported to inhibit several isoforms of CYP, this theory cannot be attributed to mangiferin's ability to upregulate P-gp expression. Therefore, more extensive and in-depth research is required to clarify the mechanism of P-gp upregulation by mangiferin.

Mangiferin is the most characteristic bioactive compound of M. indica. In addition to looking at the effect of mangiferin on membrane transporters, especially P-gp, the study conducted by Chieli et al. (2009) also used mango stem bark extract, which contains mangiferin, and the results showed that this extract was also able to affect the activity of P-gp transporters. In vitro studies using HK-2 cells treated with mango stem bark aqueous extract led to a dose-dependent reduction in P-gp activity, as measured by the intracellular Rh-123 fluorescence parameter. An increase in intracellular Rh-123 fluorescence indicates an increase in the amount of Rh-123 entering the cell. In other words, the P-gp efflux activity in eliminating the compound that serves as its substrate decreases. However, in an assay using Calcein-AM parameters, the results showed that mango stem bark extract could not increase the fluorescence in the Calcein-AM test.

Subsequent in vitro studies reported that in addition to activity, M. indica extract also modulated P-gp expression at its protein and mRNA levels.[2,19] It was reported that there was a dose-dependent reduction in the levels of P-gp transporters after administration of M. indica extract, and in parallel, it was also shown that there was a decrease in the mRNA level of ABCB1, the gene encoding that P-gp transporter. The mango plant extract did show the ability to inhibit the activity and expression of the ABCB1 gene and P-gp

protein, but due to its highly complex content, it is not yet known exactly which compound is responsible for this activity.

3.4. Epigallocatechin-3-gallate (EGCG)

EGCG (Figure 1B) is one of major catechin found in green tea plant (C. sinensis). Of all the catechins, EGCG is the most abundant (up to 59% of the total catechins) and the most studied for its biological activity as an antiviral, antibacterial, and anticancer which is stronger than other catechin-derived compounds.[28] EGCG consists of 8 phenolic groups, providing many electron acceptors and donors so that it can bind to many other molecules, especially proteins.[29] This high-affinity binding can suppress protein activity.

An in vitro study conducted by Knop et al. (2015) showed that green tea extract containing EGCG can block the transport of compounds that are substrates of the P-gp, OCT1, OCT2, MATE1, MATE2-K, OATP1B1, and OATP1B3 transporters. These all are seven vital drug transporters in intestine, liver, and kidney. EGCG alone can also inhibit all those transporters, with the highest inhibition occurring to OATP1B3. EGCG also notably inhibited cationic drug transporters. In experiments with metformin as a cationic drug, the substrates of the influx transporters OCT1, OCT2, MATE1, and MATE2-K showed a decrease in metformin uptake activity upon EGCG administration, compared to the condition when inhibitors are absent. This provides an explanation that the translocation of metformin into the cell is facilitated by OCT1, OCT2, MATE1, and MATE2-K transporters. So when given inhibitors of these transporters such as EGCG, there is a decline in the amount of metformin entering the cell.[5]

Uptake of Sulfobromophthalein (BSP) and atorvastatin that were mediated by OATP1B1 and OATP1B3 transporters was also reported inhibited by EGCG administration. This can explain the reduction in the influx activity of the transporters OATP1B1 and OATP1B3, which play a role in bringing in BSP and atorvastatin, by EGCG. Besides modulating the influx transporter, EGCG was also found to inhibit the P-gp transporter in exporting digoxin and vinblastine as its substrate in the Caco-2 cell line.[5,30] EGCG significantly reduced digoxin transport from the basement membrane to the apical membrane. Another study that examined the effect of EGCG on P-gp transporters also showed similar results, that EGCG can be a natural compound that can handle multidrug resistance problems due to the efflux activity of anticancer drugs by P-gp transporters. EGCG was reported to inhibit the efflux of Rh-123 by P-gp transporter resulted in increased substrate accumulation in Chinese hamster ovary resistant cells CHRC5 and multidrug-resistant human epidermal carcinoma cell line KB-C2.[6,30] In addition, studies also found that EGCG might be used as potential chemosensitizers because it could increase the accumulation of Rh-123 and Calcein-AM in P-gp-overexpressing Caco-2 cells and human T-lymphoblastic leukemia cell line CEM/ADR 5000, respectively, by inhibiting P-gp activity.[17] This major green tea polyphenol was also previously described as P-gp modulator that diminish both the expression and function of P-gp in HK-2 cells.[31] EGCG modulate this membrane protein possibly by

Table 2. Overview of studies of the effects of EGCG on membrane transporters

Membrane Transporter	Effects	Reference
P-gp	Inhibition of its activity in Caco-2, CHRC5, KB-C2, HK-2, and CEM/ADR 5000 cells	(5,6,17,30,31)
	Downregulation of its expression in HK-2 and HepG2 cells	(17,31,32)
BCRP	Downregulation of its expression in HK-2	(17,33)
OCT1, OCT2, MATE1, MATE2-K, OATP1B1, and OATP1B3	Inhibition of transporter's activity	(5)

binding to its nucleotide-binding domain 2 (NBD2), thereby preventing ATP binding and subsequent energy-dependent drug efflux.[34,35]

One of the mechanisms underlying the MDR phenomenon is the overexpression of P-gp transporter. A study showed that the expression of P-gp and MDR1 gene is induced by doxorubicin, one of chemoterapy medication used to treat cancer.[36] Subsequent study showed that EGCG possess an ability to downregulate doxorubicin-induced overexpression of P-gp in human hepatoma HepG2 cells.[32] Similar findings were reported by previous studies. Not only does EGCG downregulate P-gp, but it can also reduce the expression level of BCRP.[17,33]

EGCG has inhibitory effects on some membrane transporters, but this effect is still below that of green tea extract, although EGCG is the most active compounds in the extract.[5] This could be due to the role of other catechins or other secondary metabolites in the green tea extract that has a synergism effect on modulating these transporters, in this case inhibiting transporter activity. Other catechin compounds in the extract such as epicatechin, epigallocatechin, and epicatechin gallate[37] demonstrate the capability to inhibit the P-gp-mediated active efflux.[6,30] Green tea extract also contains phenolic acids such as gallic acid, which is able to inhibit P-gp function[38] and expression both at protein and mRNA level.[2] The complexity of the chemical compounds contained in an extract allows for an increase or decrease in a pharmacological effect.

3.5. Quercetin

Quercetin (3,3',4',5,7 pentahydroxy flavone) is a flavonoid in the form of a plant pigment found in various fruits and vegetables such as mangoes, green tea, apples, berries, onions, capers, red wine, and other plants (Figure 1C).[19,39] Not only is quercetin the most abundant plant flavonoid in the human diet, but it has also been widely used as a health supplement, either on its own or in combination with other chemicals. Quercetin is known for its beneficial pharmacological properties such as antioxidant, antiinflammatory, anticancer,

Table 3. Overview of studies of the effects of quercetin on membrane transporters

Membrane Transporter	Effects	Reference
P-gp	Inhibition of its activity in HK-2, KB-V1, human pancreatic carcinoma resistant to daunorubicin, and in vivo using pigs and rats	(19,43,44,45,46)
	Downregulation of its expression in HK-2, KB-V1, human pancreatic carcinoma resistant to daunorubicin	(2,43,45)
	Upregulation of its mRNA expression in Caco-2 and LS174T cells	(39,48)
	Upregulation of its mRNA expression in rat tissue intestine, but not in liver and kidney	(39)
	Upregulation of its protein level expression in Caco-2 cells	(48)
BCRP	Inhibition of its efflux activity in HeLa cells, BCRP-overexpressing HEK-293 and MDCKII cells	(40,49)
	Inhibition of BCRP activity in vivo: higher intestinal absorption of sulfasalazine (BCRP probe) in rats	(49)
MRP1	Upregulation of its mRNA and protein expression in MCF-7 cells	(50)
MRP2	Inhibition of its activity in MDCKII cells	(39)
	Upregulation of mRNA expression in vitro in LS174T cells and in vivo in rat tissue intestine, but not in liver and kidney	(39)
	Upregulation of its protein expression in Caco-2 cells	(51)
UGT1A6	Upregulation of its protein expression in Caco-2 cells	(51)
OATP1A2 and OATP2B1	Inhibition of substrate uptake in HEK293 cells	(7)

antiviral, and the prevention of cardiovascular disease.[40,41,42] On the other side, this compound has been known to interact with multidrug transporters.[19] In a study using multidrug-resistant human cervical carcinoma KB-V1, it was reported that quercetin was able to significantly increase intracellular Rh-123 fluorescence accumulation, suggesting that this compound can inhibit export function of P-gp.[43] These results were also supported by other experiments using the Calcein-AM assay. Quercetin increased intracellular Calcein-AM fluorescence dose-dependently, which at its highest concentration was able to equalize the ability of verapamil. Verapamil was used as a standard due to the drug's use as a P-gp transporter modulator.[19] In another study report, co-administration of quercetin with digoxin in pigs caused the death of two-thirds of pigs, and the others experienced acute poisoning due to digoxin. This is because digoxin is a P-gp substrate and quercetin inhibits the action of P-gp, resulting in an increase in digoxin concentration.[44] With the significant results shown by the administration of quercetin, this compound plays a critical role in P-gp transporter inhibition.

In line with its effect on the activity of the P-gp transporter, quercetin is also reported to affect the expression of the transporter, downregulating its expression in the HK-2 and KB-V1 cells.[2,43] Similar results were reported by Borska et al. (2010) that quercetin treatment to human pancreatic carcinoma cell line resistant to daunorubicin decrease the P-gp protein expression level and function.[45] Challa et al. (2013) suggested that combination of valsartan with quercetin as oral dosage could be developed. The study showed that quercetin acted as P-gp inhibitor, thus significantly increases the intestinal absorption of valsartan and decreases its efflux, in vitro and in vivo.[46]

Several heat shock elements (HSEs) are located in the promoter part of the MDR1 gene (ABCB1). This gene promoter activity can be enhanced by heat shock factor (HSF) that reported to be the key regulator of MDR1 gene expression. Quercetin, from several studies, showed its ability to suppress MDR1 gene expression by inhibiting the DNA binding activity of HSF.[47] Thus, quercetin suggested to be used to reverse the MDR phenotype by downregulating the expression of P-gp. However, another study with different cell lines showed a contradictory results. Chae et al. (2015) demonstrated that MDR1 gene were upregulated by repeated pretreatment with quercetin in Caco-2 cells, possibly via a vitamin D receptor-dependent pathway.[48]

BCRP is another efflux transporter involved in MDR that reported to be influenced by quercetin administration. An in vitro study using BCRP-overexpressing human embryonic kidney (HEK293) cells demonstrated that quercetin inhibit BCRP, indicated by increased accumulation of BCRP substrate SN-38.[40] Similar results reported by Song et al. (2020) using human cervical cancer HeLa cells, which quercetin dose-dependently enhanced the intracellular accumulation of the BCRP substrate, mitoxantrone. Consistently, the bidirectional transport assay using BCRP-overexpressing MDCKII cells resulted in a significant reduction of transcellular efflux of prazosin, another BCRP substrate.[49]

Not only inhibits transporters, but on the contrary, quercetin is also reported to induce other membrane transporters. Studies on human breast cancer Michigan Cancer Foundation 7 (MCF-7) cells induced by quercetin at concentrations of 50 and 100 µM for 48 h showed increased mRNA and protein expression of the MRP1 transporter.[50] The protein expression of MRP2 and UDP-glucuronosyltransferase UGT1A6 in Caco-2 cells induced by quercetin for 72 h also increased.[51] An in vitro study conducted by Oh et al. (2019) evaluated the induction and inhibition of MRP2 by quercetin in Madin-Darby canine kidney II (MDCKII) cells and human colonic adenocarcinoma LS174T cells using phenolsulfonphthalein (PSP) as MRP2 substrate. In MDCKII cells, quercetin demonstrated a notable inhibitory effect on MRP2 at a concentration of 10 µM. In LS174T cells, quercetin at a concentration of 50 µM increased the mRNA expression of MRP2 by 3.0-fold, compared to the control; while the mRNA expression of P-gp was also

upregulated with the administration of 50 μM quercetin. The increase was greater than that produced by MRP2's known inducer, vincristine. This study also suggests that prolonged exposure to quercetin alters the MRP2 gene expression and its function at the cellular level. However, an in vivo assay to see the effect of quercetin administration conducted for 7 days using rats showed no change in Mrp2 and Mdr1a (orthologs of human MDR1) mRNA expression in the liver and kidney but increased in the intestine. The largest increment in mRNA expression was observed at the dose of 100 mg/kg, where the expression was increased by 15.4-fold for Mrp2 and 5.8-fold for Mdr1a.[39]

3.6. Kaempferol

Kaempferol (Figure 1D) is a flavonoid compound that is widely found in mango, spinach, kale, ginkgo biloba, black tea, green tea, onion, broccoli, and other vegetable crops.[43,53] The highest amount of kaempferol was found in leek and endive.[7] From several studies that have been conducted, kaempferol is reported to reduce the expression of P-gp and the efflux activity, based on the Rh-123 fluorescence test. The experiment results were also confirmed by other assay, which showed that kaempferol could increase the cellular accumulation of 3[H]vinblastine, a radioisotope-labeled drug, in cells in a dose-dependent manner. In addition, it was also reported that there was a decrease in the efflux of 3[H]vinblastine from the cells. Besides modulating the efflux function, kaempferol also reduced the expression of P-gp protein in the KB-V1 cell line.[43]

The study conducted by Mandery et al. (2010) found that administration of kaempferol in HEK293 cells affects the transport of BSP, atorvastatin, and fexofenadine mediated by OATP1A2 and OATP2B1, two transporters that are located in the apical membrane of enterocytes and can affect the intestinal absorption of orally administered drugs. Kaempferol inhibited those transporters-mediated uptake of substrates into HEK293 cytoplasm likely through a competitive mechanism.[7] Kaempferol also showed the ability to inhibit glucose uptake by Glucose-transporter 1 (GLUT1), which in turn inhibits the survival and proliferation of tumor cells because glucose is an extremely important compound for both of these stages. Apart from inhibiting GLUT1 activity, kaempferol also lowers its mRNA expression levels by 40%. This capability highlights the potential of kaempferol as an anticancer agent.[52]

4. Conclusion

Membrane transporters are proteins found in all organisms and serve a crucial function in controlling the influx of essential nutrients and ions as well as the efflux of cellular waste compounds, toxins, and xenobiotics including drugs and bioactive compounds. In addition to regulating the movement of substrate compounds in and out of cells, membrane transporters are also controlled or influenced by various factors, including drugs or bioactive compounds from natural materials that can be inducers or inhibitors of the transporter's activity. Not only that, drugs or bioactive compounds can also modulate the expression of transporters, at the mRNA and/or protein level.

The use of mangiferin, EGCG, quercetin, and kaempferol can lead to interactions and modulation of membrane transporters (Table 1-4). Polyphenols have a common pharmacological chararacter which is pleiotropic effect towards protein. The phenolic hydroxyl groups in their

Table 4. Overview of studies of the effects of kaempferol on membrane transporters

Membrane Transporter	Effects	Reference
P-gp	Inhibition of its activity and downregulation of its protein expression in KB-V1 cells	(43)
GLUT1	Inhibition of substrate uptake and reduction of mRNA expression levels	(52)
OATP1A2 and OATP2B1	Inhibition of substrate uptake in HEK293 cells	(7)

structure can partly dissociate to negatively charged phenolate ions. Then there will be multiple hydrogen and ionic bonds between dissociated polyphenols and various protein. Thus theoretically, it will inhibit the protein's function.[17] However, polyphenols do not exhibit the same effects on all cells. Its pleiotropic effects depends on several conditions such as type of tumour, redox status of cells, ATP concentration, and/or exposure time and concentration of the compound.[45]

Inhibition of the ABC transporter can indeed be a solution for poor drug bioavailability, especially for drugs that are poorly absorbed or to reverse MDR phenomenon. But on the other hand, this inhibition can also enhance the toxicity of toxic compound or drugs with narrow therapeutic window that can actually be expelled from the cell by the ABC transporter. So, it is all depends on the transported compound. In addition, in a long-term, inhibition of P-gp might also increase the risk of renal disorder.[21]

Studies on the impacts of these bioactive compounds is important in considering co-administration with some drugs, as they may affect drug levels in cells. In addition, inhibition of the P-gp transporter can be utilized in the treatment of the multidrug resistance phenotype. But as membrane transporter not only involved in tumor cells MDR, but may also affect various drugs, bioactive food ingredients, and toxic compound bioavailability in organisms,[22] it is important to carefully consider consuming foods or supplements containing mangiferin, EGCG, quercetin, kaempferol, or other flavonoids, especially when taking medication.

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