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Natural polyphenols: Influence on membrane transporters

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ABSTRACT

Accumulated evidence has focused on the use of natural polyphenolic compounds as nutraceuticals since they showed a wide range of bioactivities and exhibited protection against variety of age-related disorders. Polyphenols have variable potencies to interact, and hence alter the activities of various transporter proteins, many of them classified as anion transporting polypeptide-binding cassette transporters like multidrug resistance protein and p-glycoprotein. Some of the efflux transporters are, generally, linked with anticancer and antiviral drug resistance; in this context, polyphenols may be beneficial in modulating drug resistance by increasing the efficacy of anticancer and antiviral drugs. In addition, these effects were implicated to explain the influence of dietary polyphenols on drug efficacy as result of food-drug interactions. However, limited data are available about the influence of these components on uptake transporters. Therefore, the objective of this article is to review the potential efficacies of polyphenols in modulating the functional integrity of uptake transporter proteins, including those terminated the effect of neurotransmitters, and their possible influence in neuropharmacology.

KEY WORDS: Herb-drug interactions, membrane transporters, polyphenols, therapeutic application

INTRODUCTION

Polyphenols encompass several classes of compounds that produced in plant as secondary metabolites, and they were routinely consumed with human diet. Until now, about 7000 different chemical molecules together with their metabolites were identified in many types of fruits and vegetables [1]. They received increasing attention due to their well-documented therapeutic significance in many diseases and disorders [2]. Chemically, all polyphenols have one or more hydroxylated aromatic rings that account for both structural and physicochemical properties, and allow their classification into several chemical classes including lignans, flavonoids, stilbene, isoflavones and phenolic acid derivatives [1]. All polyphenols have reducing properties; they can donate hydrogen to oxidized cellular constituent, and play a significant role against oxidative stress-related pathologies, like cardiovascular diseases, cancer and variety of neurodegenerative disorders [3]. Moreover, many *in vitro* and *in vivo* studies suggested that the beneficial effects of polyphenols extended to involve cell signaling, since they act as regulatory factors of gene transcription that affect many important processes like cell growth and apoptosis [4-7]. Flavonoids are the most abundant polyphenols that widely consumed by peoples worldwide; therefore, many researchers focused on the effects of many flavonoids like resveratrol [8], quercetin, epigallocathechin-3-gallate (EGCG), rutin and curcumin, as a health promoting compounds in treatments of several diseases [9-11]. However, low bioavailability of most polyphenols represents the main hurdle in their use as dietary supplements. Bioavailability of polyphenols is closely related to the biotransformation process, which mainly based on Phase II conjugation reactions of the free hydroxyl groups with methyl group, sulfate or glucuronic acid [12,13]. The diversity in polyphenols structure increases the possibility of different interaction patterns with membrane transporters at different anatomical sites [14,15]. The balance between absorption and excretion of dietary polyphenols can be achieved by modulation of the tissue uptake system, suggesting that certain cells may readily incorporate them by specific mechanisms; for instance, morin can cross the vascular endothelium by a rapid, energy-dependent transport system that can also transport other hydroxylated compounds [16,17]. Recently, kinetic studies showed that the functional integrity of both uptake and efflux transporters represent the basis behind different tissue

distribution of orally administered drugs in certain organs such as liver, kidney, and brain in animals that chronically challenged with polyphenolic compound, and reflects the importance of these transporters as a site for food-drug interactions [18,19]. On the other hand, such interaction can be utilized for treatment of central nervous system (CNS) related disorders like depression, anxiety, and other psychoneuronal diseases associated with functional abnormalities of monoamine transporters (MATs) [20]. Accordingly, polyphenols may be considered as a potential modulators that can maintain homeostasis within brain tissues, and provide adaptation against neuronal stress [21,22].

PLASMA MEMBRANE TRANSPORTERS

To maintain the normal cell functions, transport of organic and inorganic molecules across the lipid bilayer of the plasma membrane is vital for life and maintenance of homeostatic mechanisms [23]. It represents a tough barrier for most polar molecules, while enables passage of hydrophobic molecules only through passive diffusion [24]. Transport of ions, polar organic compounds, in addition, to the transport against concentration gradient of many chemicals (e.g., nutrients and metabolites) requires a special transport system that rely on a source energy utilized either through the existed potential of chemical gradients or coupled with enzymatic reactions that consume anion transporting polypeptide (ATP) [25]. With few exceptions, transport substrates of the rotary motor and P-type ATPases are limited to metal ions or protons; however, ATP-binding cassette (ABC) type transports a broad range of substrates, including amino acids, sugars, nucleosides, vitamins, peptides, lipid molecules, oligonucleotides and polysaccharides [26,27]. There are more than 1300 membrane transporter proteins that are broadly classified into efflux and influx types relative to the direction of substrate flow. Moreover, utilization of energy for transportation allow further sub-classification into active and passive transporters [28]. The group of active transporters included three subclasses, primary, secondary and tertiary depending on their driving force, which could be either ATP or the chemiosmotic gradient [29]. These transport systems are mostly substrate-specific and saturable, and can be competitively or noncompetitively blocked, and genetically regulated. In addition, active membrane transport is vectorial, where the substrate is either transported into or out of the cell; however, the same transporter does not perform both actions [30,31]. In general, the term active transporters cover the following:

i. ATP-binding cassette protein (ABC): Members are mainly expressed on the membrane of excretory organs, where they regulate extrusion of wide range of chemically different substrates against electrochemical gradient to the extracellular region. This group includes seven subfamilies represented by ABCA, ABCB which also known as p-glycoprotein (P-gp) or multidrug resistance (MDR), ABCC or MDR proteins, ABCD, ABCF and ABCG which include breast cancer resistance protein (BCRP or ABCG2) [32,33].
ii. The solute carrier (SLCs) transporters or uptake transporters: Members are mainly located in cell membrane of organs having tubular lumen structures like liver, kidney and intestine; they were organized into more than 50 families and have chemically related substrate specificity. They transported diverse substrates including charged and uncharged organic molecules, in addition to inorganic ions. The most characterized families of this class are the organic ATPs (OATPs), which include OATP1, OATP2, OATP3, OATP4, OATP5, and OATP6 [34,35]. In addition, the organic anion transporters (OATs), which include seven members represented by OAT1, OAT2, OAT3, OAT4, OAT6, OAT7 and OAT10, perform the transport of substrates with molecular weights of 400-500 Da. Meanwhile, the organic cations transporters (OCTs) include twenty members, some are well identified like OCT1, OCT2, OCT3, OC12 and the organic creatinine transporters, where the latter is recently included and involved in bidirectional transport of creatinine to maintain its physiological level [36]. In aeneral, OCTs catalyzed transport of monoamines neurotransmitters, Zwitter ions, and some anion substrates with different tissue distribution [37-39]. Since SLTs have regulatory role in absorption, uptake and elimination of different drug molecules, trace elements and dietary nutrients, they are considered as important site of kinetic drug-drug and/or drug-nutrient interactions, where modulation of their function can influence the availability and therapeutic efficacy of many ligands including drugs and other health promoting supplements [40].
iii. MATs: This class included three members of membrane transporters (NET, SET and DAT), which catalyze transport of norepinephrine, serotonin, and dopamine. They are expressed at the presynaptic area within both CNS and the periphery [41], and involved in regulating neurotransmission, utilizing Na/Cl gradient as driving energy that induce conformational changes to enhance uptake and release of monoamines [42,43]. In spite of functional importance of peripheral MATs, no sufficient information are available compared to those present in CNS, which have been widely studied [44]. Impairment of neurotransmitter homeostasis is correlated with many CNS disorders such as depression, anxiety, attention deficit hyperactivity disorder, schizophrenia, and Parkinson's disease [45], and suggests MATs as important therapeutic targets. In this regard, treatment of depression has been focused on modulating monoamine neurotransmission, mainly achieved through blockade of MATs [46]. Meanwhile, development of non-selective tricyclic antidepressants, selective serotonin reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors is the most valuable outcome of this concept [47]. Moreover, drugs of abuse including cocaine and amphetamines interfere with MATs; accordingly, these transporters are considered as potential targets for treatment of drug addiction [48]. Dysfunction or complete deletion of DAT showed to decrease the clearance of dopamine that associated with spontaneous hyperactivity, sleep disturbances, motor deficiency, and cocaine abuse behavior [49]. Meanwhile, deletion of NET in animal models showed resistant depressive-like effects of stressors with anti-nociceptive activity, and such models were less vulnerable to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-

induced neurotoxicity [50]. The contribution of central serotonin in controlling mood and behavior was reported using SET-deficient rats, and anxiety could be ameliorated by a 5-HT1A antagonist [51]. Another study revealed that depletion of serotonin level in gastrointestinal tract (GIT) was observed in patients with irritable bowel syndrome that often associated with increased expression of SET in the colon, suggesting the role of SET inhibitors in its treatment [52,53].

INTERACTIONS OF NATURAL POLYPHENOLS WITH MEMBRANE TRANSPORTERS

Numerous data have summarized the broad biological properties and the diversity of polyphenols targets in the biological systems that mediate their activities. Both chemical structure and the nature of interaction of polyphenols with biomembranes are critical for their beneficial effects, and such interaction represents the underlying mechanism through which they affect the functional properties of membrane bound enzymes and transporter proteins, which alter transmembrane potential for endogenous and exogenous molecules [54]. Dietary polyphenols became increasingly popular, and some of them have a potential role in initiating adverse drug interactions that may be established through alterations in efflux and uptake transporters [55]. Similar to conventional drugs, many natural ingredients, including polyphenols, interact with various classes of drug uptake transporters. For example, the flavonoids apigenin, quercetin, and kaempferol block the transporter functions of OATP1A2 and OATP2B1, which are localized in the apical membrane of the intestinal lumen [56]. Furthermore, green tea catechins, herbal extracts, and citrus and grapefruit juice affect the OATP-mediated transport of many ligands [57-59].

INTERACTIONS OF NATURAL POLYPHENOLS WITH MDR TRANSPORTERS

MDR transporters are family of proteins that include P-gp as an important member, which was primarily characterized in MDR Chinese hamster ovary (CHO) cells. P-gp transports xenobiotics outward in a unidirectional pattern utilizing ATP as energy source [60]. Other MDR-related transporters were discovered within different types of cells such as MDR related proteins (MRP's) [61] and BCRP-1 [62]. Ligands that inhibit these efflux transporters were expected to elevate the intracellular concentrations of many therapeutic agents in similar fashion to P-gp blockade [63]. In addition to the potential role of P-gp in normal physiological processes, its overexpression on cancer cells decreases significantly the intracellular concentrations of a many chemotherapeutic agents [64]. It has been reported that natural polyphenols or their synthetic analogs can modulate the MDR transporters responsible for chemotherapy resistance, including P-gp, MRP1, and BCRP [65]. Flavonoids and stilbenes are known as the third generation of P-gp blockers and produce comparable effects to those of the already known P-gp inhibitors like verapamil and cyclosporine [66]. Many flavonoids have the capacity to inhibit BCRP; thus, consumption of flavonoids with high blocking activity can modify pharmacokinetics and levels of drugs that are extruded by BCRP [67]. In addition, many polyphenols are well-known as P-gp blockers including EGCG that down-regulates P-gp and BCRP but did not inhibit MRP1 in a tamoxifen resistant breast cancer cell line [68]. Other polyphenols with hydrophobic groups like prenyl substituents may be the future promising candidates for MDR reversal agents.

The activity of P-gp can be modulated by altering the physical state of the surrounding lipids and/or lipid composition. Polyphenols, including biochanin A, morin, phloretin, and silymarin, have been reported to influence the transport activity of ABCB1 protein. These effects resulted in a significant increase of daunomycin accumulation in P-gp expressing cells in a concentration-dependent manner, and explained by the competitive binding of the polyphenols to the ligand binding site on the P-gp molecule that end up with drug accumulation [69]. Others reported that quercetin inhibits the ATPase activity of P-gp, a mechanism that based on structural properties of this polyphenol [70]; however, the mechanism through which genistein modulates drug transport across plasma membrane seems different, where its interaction with MRP1 increased daunorubicin accumulation in cell lines overexpressed MRP1 without expression of P-gp [71]. In other studies that utilize membrane vesicle preparations to evaluate the direct inhibition of MRP1, polyphenols interact with various sites on the MRP1 molecule. In addition, they showed an increase in the activity of cystic fibrosis transmembrane conductance regulator (CFTR; ABCC7) chloride channel [65,72,73]. Catechins were also found to interact with P-gp and can modulate its transport activity relative to the type of tested compound, where some of them affect the fluorescent markers transported by P-gp, while others increase the transport of these markers [74]. Polyphenols like mangiferin and the mangiferin aglycone derivative norathyriol, as well as catechin, gallic acid and quercetin were investigated for their potential ability to influence ABCB1 gene and P-gp expression in HK-2 cells. Western blot analysis demonstrated a time and concentration-dependent modulation in P-gp activity that correlated to relative changes in the ABCB1 mRNA content [75]. Resveratrol, a well-known polyphenol, was found to improve the cytotoxic profile of docetaxel and doxorubicin in solid tumors through blockade of P-gp efflux and down-regulation of MDR1 gene [76]. More recently, silibinin dihemisuccinate improves the sensitivity of methotrexate-resistant human rhabdomyosarcoma cell lines to the cytotoxic activity of methotrexate in concentration-dependent pattern, most probably through modulation of methotrexate transport through the plasma membrane [77].

INTERACTION OF NATURAL POLYPHENOLS WITH UPTAKE TRANSPORTERS

Oral drug delivery is the most acceptable way of administration, mainly because of patient compliance and ease of administration. Many studies have suggested the role of specific transporters in GIT absorption of weak acids. In clinical practice, patients usually administer various types of drugs at the same time.

Thus, drug-drug interactions that involve membrane transporters may directly affect safety and efficacy of many drugs and food components. It has been reported that ferulic acid, widely used as a functional food, modulates the transport of many clinically effective agents, and baicalin inhibits the specific transport system that mediate transport of the active metabolite of irinotecan through the intestinal epithelium and ameliorate severe diarrhea associated with high doses of this compound [78,79]. Inhibition of OATP2B1 by polyphenols in apple juice may also contribute to limit drug-induced GIT toxicity, and may be of value in prophylaxis of late-onset diarrhea reported during CPT-11 therapy [80]. Herbal extracts and dietary polyphenols were investigated for their broad bioactivities including maintenance of glucose homeostasis, neuroprotection and regeneration, which often attributed to the functional control of uptake transport processes [81]. Tea polyphenols showed tendency to attenuate degeneration of dopamine neurons and toxicity induced by 6-OHDA and MPP by mechanisms not only related to anti-oxidant or metal-chelating properties, but may be directly mediated by modulation of transporters and intracellular signaling pathways [82]. Polyphenols are studied for their potential to alter the kinetic properties of other chemicals, mostly through their influence on metabolism and/or transportation at different tissue levels relative to their distribution. To date, few number of transporters were studied for their interaction with dietary polyphenols [56,83]. Although the precise molecular mechanisms by which polyphenols interact with uptake transporters are not well identified, several *in vitro* studies on cell lines expressing MATs revealed that polyphenols could interact with membrane functional proteins, like enzymes and/or transporters, as competitive or non-competitive ligands through direct interaction with the active or allosteric sites, altering their configuration and functional activity [84]. The tea polyphenols ECG and EGCG are good ligands for OATP1B3 and OATP1A2 that widely expressed in liver and intestinal epithelium [59], and they can inhibit the uptake of dopamine and MPP^+ by DAT, thus protected embryonic rat mesencephalic dopaminergic neurons against MPP^+-induced injury [85]. Moreover, an *in vitro* study showed that quercetin rather than naringin can specifically transported by intestinal OATP2B1 expressed in Caco2 cell line, and specific inhibition of these transporters can reduce uptake of quercetin. However, the conjugated polyphenols, as sulfated conjugates, were effectively taken up by OAT1 and OAT3 [86]. In neuropharmacology, the mechanisms by which polyphenols and their metabolites cross the blood-brain barrier (BBB) remain a hot spot for future research. Many *in vitro* studies evaluated the neuroprotective effects of polyphenols, and many evidence suggested that both aglycones and the conjugates behaves as ligands for OAT to cross the BBB. Such transport mediated by OATs and OATP1A2 may influence brain tissue levels of the administered flavonoids. In a kinetic study, galangin and apigenin competitively inhibit A and B isoforms of MAO, while other polyphenols showed antidepressant effect by altering transportation of NE and SE [87]. The medicinal herb hypricum, contained 6-15% of proanthocyanidin and 5% phenolic acid, was known to exert antidepressant effect by non-competitive reuptake inhibition of monoamines; however, its therapeutic potential remain questionable due to its poor bioavailability [88]. The sensitivity of membrane transporters to polyphenols was examined in comparison with bupropion, a reference inhibitor for both DAT/NET, using recombinant technique for CHO cell line expressed these transporters. The results showed that polyphenols have selectivity to inhibit MATs, with high potency and efficacy for DAT and NET more than SET, indicating competitive inhibition of DAT/NET [89]. Moreover, cells expressing OAT1 showed increasing tendency to the uptake of the aglycone silibinin three folds than control cells [90]. *Ginkgo biloba* flavonoids including kaempferol, quercetin and apigenin showed competitive inhibitory effect of OATp1B1 and OATp1B3 expressed on HEK293 cell line, with no significant effect on OCT [91]. In a study that investigates the role of hepatic MRP_2 in the disposition of polyphenols, both MRP_2 and BCRP exhibited an essential role in the efflux of glucuronidated quercetin and naringin [83]. Interestingly, hesperidin and EGCG enhance the activity of the clinically used benzodiazepine through a modulatory effect on GABA-A receptor where they bind two sites [92]. These modulatory effects of polyphenols may guide pharmacological research to develop natural products with therapeutic benefit for treatment of depression or other neurological disorders, besides their implication in drug-dietary supplement interactions [93]. On the other hand, polyphenols may act as modulators of transporter proteins directly by either increasing or decreasing the activity of membrane proteins, or indirectly by modifying the signaling pathways and expression of mRNA encoding these transporters. It has been shown that individual components of silymarin showed a significant but different inhibitory effect on OATp transporters in overexpressing cell lines in spite of their structural similarity and identical molecular weight; this finding revealed the influence of stereochemistry in modifying the interaction potential with OATP transport proteins, as observed from variable values of IC50 among these components [94]. Other study showed that both morin and silibinin competitively inhibit OAT1 with IC50 values of 0.5 and 25 μM, respectively, while ellagic acid was a potent inhibitor of OAT1 activity with IC50 of 207 nM [90,95]. Assessment of the modulatory effect of red wine polyphenols like resveratrol, quercetin and myricitin, using MPP^+ as a reference substrates for OCT1 and OCT3 in Caco2 cells expressing these transporters, indicated that these polyphenols increased the uptake of MPP^+ in a concentration-dependent manner, just like the effect of grape seed proanthocyanidins [96,97]. Moreover, other investigators showed that myricetin and catechin decrease MPP^+ uptake more than quercetin which displayed strong inhibitory effect [98]. In 2010, Zhao *et al* suggested that the cytoprotective effect of polyphenols could be mediated through modulation of the MATs, where both transgenic CHO and dopaminergic cell line (wild type) that specifically transported monoamines used to investigate the effect of the frutescens fruit polyphenols luteolin and apigenin. Both provided a significant increase in the uptake of DA and NE, with higher potency of luteolin over apigenin. These effects may be a consequence of conformational changes or translocation of transporter proteins induced by polyphenols. In addition, luteolin can counteract the inhibitory effect of cocaine, the competitive inhibitor of DAT. Thus, luteolin had

tendency to give antipsychotic and anti-addictive effects [99]. Inhibitors of SET were known to prolong neuronal signaling of serotonin to improve depression and control intestinal function. Investigation of polyphenols that founded in licorice like methyl glabridin, glabridin and glabrene using HEK-293 cell line expressing SET showed 53%, 60% and 47% inhibition of SET, respectively, suggesting the impact of dietary polyphenols on mood through modulation of SET [100]. To date, little information are available about expressional modulatory effect of polyphenols. It has been postulated that stress signals induced down-regulation of OAT1 and OAT3, while treatment of cell lines expressing these transporters with curcumin results in two folds up regulation of these transporters, and reduced the expression of OATP1B1 [101]. The isoflavon genisten was reported to decrease expression of NE uptake transporters in human neoplastoma cells, suggesting its potential pharmacological action of on sympathetic neurons [102]. The polyphenols of *Cynomorium songaricum* extract were investigated on CHO expressing MAT, and the results indicated that they inhibit DAT/NET transporters; however, more polar fractions possess dual glutamate/serotonin transporters inhibition suggested the multi-spectrum targeting effect of these polyphenols [103]. For instance, the multifunctional modulation of cell signaling pathways in neuroprotection activities of tea polyphenols was investigated using 6-OH-DA model of PD, where they decrease apoptosis through increasing the anti-apoptotic signaling proteins [104].

The classic concept of transporters in the CNS illustrated mechanisms that control many functions in the brain, including autonomic function, locomotion, hormones secretion, and behavioral and intellectual activities related to the emotion and reward [105]. Moreover, functional disturbances of these transporters predispose various CNS pathologies [43]. During neuronal transmission, the intensity and duration of synaptic signaling are determined, in part, through the reuptake of the signaling molecules through specific membrane-bound transporters, which are mostly belong to the SLC6 family [106]. In certain circumstances, these transporters can transport other substances including drug molecules and toxins, which may be associated with positive or negative modulation of their original function. In this regard, dopamine transporters enabled the transport of molecular toxins, such as MPP^+, 6-hydroxydopamine [107], and paraquat [108] into the dopaminergic neurons leading to selective dopaminergic neuron damage. Many researchers have reported the influence of polyphenols on DATs; pretreatment of mice with 7,8-dihydroflavone significantly attenuated the reduction of DATs in the striatum after repeated doses of methamphetamine [109], and consequently reduced the associated behavioral abnormalities and neurotoxicity. In certain occasions, DATs behave as molecular ports that accumulate neurotoxins and can be modulated by EGCG, and this effect is considered neuroprotective against MPP^+-induced neurotoxicity. Based on real time-PCR data, EGCG did not interfere with the transcription of DAT mRNA, suggesting direct inhibitory effect on DAT, probably through modulating its internalization to activate PKC [110].

In concentration dependent pattern, both cis and trans resveratrol interfere with the uptake of noradrenaline and 5-HT in rat brain, suggested this polyphenol as a potential source for many CNS acting drugs, including antidepressants [111]. The natural polyphenol hispidulin produced anticonvulsant activity through the inhibition of glutamate release from cortical synaptosomes, mostly through the blockade of presynaptic voltage-dependent Ca^{+2} channels [112]. Moreover, the neuroprotective effect of procyanidin against ischemic injury was attributed to attenuating the reduction in glutamate uptake mediated through interference with the ATP required for active reuptake at mitochondrial level [113]. Similar effect was observed for myricetin and quercetin in oxygen/glucose deprivation induced swelling in C6 glial cells [114]. In another model of injury of astroglial cells, EGCG significantly increases glutamate uptake in C6 glial cells, and this may contributes to the neuroprotective role of glial cells during excitotoxicity [115]. Other types of polyphenols, including luteolin and apigenin can act as activator of MATs, which might have positive impact on many hypermonoaminergic psychological disturbances, especially during cocaine addiction [99]. Currently available data clearly showed that natural products may be of therapeutic benefits in many experimentally-induced neurological disorders. Recently, many studies shed a light on natural polyphenols that may have therapeutic significance in the prevention and treatment of many specific neurological disorders. For example, berberine, curcumin, honokiol, and tanshinone IIA, were capable to cross the BBB and protect brain tissue against damage in various animal models of neurological disorders [116-118]. These plant-derived polyphenols also have been demonstrated to decrease glutamate release in rat brain tissues [119-122]. In summary, dietary polyphenols may influence a person's mood and improve quality of life. Several *in vitro* studies using cell line expressing uptake transporter proteins showed different potencies of polyphenols to modulate transporter proteins including MAT, especially NET, SET and DAT, either directly or indirectly. In this respect, the amount and duration of polyphenols consumed with diet may be the underlying factor involves modulation of both function and expression. This, in turn, could affect the bioavailability, distribution and transport of various substrates handled by these transporters. Understanding interactions of polyphenols with transport proteins seems to be a pre-request to predict the structures of potential flavonoid-based drugs and match with the desired biological effects. Moreover, this knowledge aid in prediction the possible side-effects associated with flavonoid usage to be minimized. Actually, challenge ahead and further research required to establish the exact mechanism and determine whether polyphenols and/or metabolites have an efficacy in treatment of disorders related to uptake transporters.

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