Bioactive Flavonoids as ABC Transporters Inhibitors for Reversion of Multidrug Resistance in Cancer

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Drug resistance is a common clinical problem that occurs in patients suffering from infectious diseases and in patients suffering from cancer [1,2]. Multidrug resistance (MDR) is frequently associated with over expression of ABC transporters. This class of membrane proteins uses the energy of ATP hydrolysis to actively pump metabolites or xenobiotics out of cells against a concentration gradient. If members of this family are over expressed in chemotherapay-resistant tumor cells, they cause a remarkable decrease in cytoplasmic concentrations of chemotherapeutic agents. The ABC transporters that have been identified to play an important role in MDR are P-glycoprotein (P-gp, ABCB1), the breast cancer resistance protein (BCRP, ABCG2), and the multidrug-resistance-associated protein 1 (MRP1, ABCC1). A possible strategy to reverse ABC-transporter-mediated MDR is the inhibition of these proteins by inhibitors, also called modulators [2].

Plants and marine microorganisms are the best natural sources for identification of novel bioactive molecules. Flavonoids constitute are the main group of polyphenolic compounds present in plants as well as marine bio source. More than 6500 of various flavonoids of plants have been reported to this date [3,4]. Flavonoids differ mainly by the structure of their ring C (oxidation status and substitution) and they are classified into several subclasses such as flavones, isoflavones, flavanols, flavonols, flavonones, chalcones, etc. In the last 15 years, flavonoids, being non-toxic natural products, have attracted attention as ABC transporter inhibitors for the reversion of multidrug resistance in cancer (Table 1).

ABC transporter commonly contains several hydrophobic transmembrane domains (TMDs) on the cell membrane. Membrane outside domain was glycosylated and two nucleotide binding domains 1 & 2 (NBDs) are internal of cell membrane. These TMDs form channels for substrate drugs. These NBD domains are participate in ATP binding and hydrolysis at ATP binding site. Some of the flavonoids bind in ATP binding site prevents ATP utilization leads to inhibition of ABC transporter efflux (Figure 1).

Flavonoids are the widely distributed natural chemical constituents, which have been reporting as drug transporters inhibitors (Table 1). Apigenin, Biochanin, Chrysin, Daidzein, Epigallocatechin (EGC), epigallocatechin-3-gallate (EGCG), Fisetin, Genistein, Hesperetin, Kaempferol, Luteolin, Morin, Myricetin, Naringenin, Naringin, Phloretin, Phloridzin, Quercetin, Silibin, Silymarin are the different kind of flavonoids which are reported to be BCRP inhibitors. Among those Chrysin and biochanin A are the most potent BCRP inhibitors, producing significant increases in mitoxantrone accumulation in BCRP over expressing cancer cell lines (Figure 2.) [5].

Flavonoids have been subjected to various chemical modifications in order to obtain better P-glycoprotein inhibitors [5]. In general, it was found that modifications that increased hydrophobicity of the molecule such as prenylation or geranylation significantly increased the modulatory activity of flavonoids [6].

According to this observation, 8-prenylnaringenin turned out to be an effective inhibitor of rhodamine 123 transport in human adenocarcinoma cells [7]. Phytoestrogens are flavonoids with weak estrogenic activities, were reported as ABC transporter inhibitors [8,9].

Table 1: BCRP/P-gp inhibitors from natural sources for the reversal of multidrug resistance in cancer.

<table>
<thead>
<tr>
<th>Type of ABC transporter</th>
<th>Researcher, year</th>
<th>Inhibitors from natural sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-gp</td>
<td>Kitagawa et al., 2005</td>
<td>Acacetin, Galangin, Myricetin, Morin, Biochanin A and Kaempferol</td>
</tr>
<tr>
<td></td>
<td>Critchfield et al., 1994</td>
<td>Apigenin, Fisetin, Rutin</td>
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<tr>
<td></td>
<td>Zhu et al., 2001</td>
<td>Tea polyphenols</td>
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<tr>
<td>BCRP inhibitors</td>
<td>Imai et al., 2004</td>
<td>Phytoestrogens (Flavonoids)</td>
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<tr>
<td></td>
<td>Ahmed-Belkacem et al., 2007</td>
<td>Bioeravinones G and H (two rotenoids) from Boerhaavia rotundifolia</td>
</tr>
<tr>
<td></td>
<td>Shuzhong et al., 2004</td>
<td>Apigenin, Biochanin, Chrysin, Daidzein, Epigallocatechin (EGC), epigallocatechin-3-gallate (EGCG), Fisetin, Genistein, Hesperetin, Kaempferol, Luteolin, Morin, Myricetin, Naringenin, Naringin, Phloretin, Phloridzin, Quercetin, Silibin, Silymarin</td>
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Figure 1: Schematic representation of P-glycoprotein and flavonoids binding on ATP binding sites for inhibition (represented with arrows).

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Received December 26, 2013; Accepted December 27, 2013; Published December 31, 2013


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Salicornia herbacea 3-O-β-D-glucoside were isolated from various biological activities [10-13]. Isorhamnetin 3-O-β-D-glucosides, and quercetin have been reported for various biological activities. Marine bioactive flavonoids have been reported for various biological activities especially flavonoids, and quercetin 3-O-b-D-glucoside were isolated from Thalassia testudinum leaf [16]. Thus marine natural products especially flavonoids have great scope in future discovery as ABC transporter inhibitory drugs for reversion of multidrug resistance in Cancer.

References


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