INTRODUCTION

Bilirubin (BL) is a yellow-orange pigment resulting from the catabolism of hemoglobin. This tetrapyrrole metabolite belongs to one of the most conserved superficialities of molecules in living organisms. BL has been found to be a sensitive marker for different pathologies, such as liver cirrhosis, hepatocellular carcinoma, and hepato-biliary diseases. The enzyme that catalyzes the BL metabolism is the uridine diphosphate (UDP) glucuronosyltransferase (UGT). UGTs are a family of enzymes that catalyze the conjugation of BL to glucuronic acid, resulting in the formation of water-soluble conjugates that can be excreted in the bile. The genetic polymorphism of UGTs can affect the excretion rate of BL and its concentration in the blood, which is related to the risk of developing different liver diseases.

At high concentrations, as described in children with Crigler-Najjar syndrome type 1 (CN-I) or type II (CN-II), BL can be extremely toxic. However, in the past 20 years, the possibility of using dietary and/or medicinal plants to decrease the severity of this syndrome has increased. The use of dietary compounds that can decrease BL concentrations has been increasingly studied, as well as the role of medicinal plants in this process.

METHODS AND MATERIAL

Some studies point out that UCB may prevent cardiovascular disease (CVD) and other chronic diseases. Clinical evidence indicates that the hyperbilirubinemic individuals with GS, with mild hyperbilirubinemia, are at reduced risk of developing cardiovascular and chronic kidney disease. There are currently several studies that have established an association between low BL and the presence and severity of various cardiovascular diseases and the respective causes of end-stage renal disease such as, type 2 diabetes, metabolic syndrome, hypertension, chronic kidney disease and albuminuria. It was observed the same association, as described above, with other disease conditions which physiology is related to oxidative stress, such as rheumatoid arthritis, multiple sclerosis, cancer and overall mortality.

DRUG INTERACTION WITH BILIRUBIN METABOLISM

Many exogenous substances, xenobiotics and drugs are substrates of UGT1A enzyme. Genetic variations that alter the expression of UGT1A may play a major role in toxicity for patients. The variation most studied in this interaction corresponds to the polymorphism UGT1A1*28, as the UGT1A promoter region responsible for the GS, characterized by hyperbilirubinemia. Examples of UGT1A substrates are alcohol (SN-98), zacrinonato and urcinato (6).

RESULTS

An extensive variety of fruits and vegetables offer a range of nutrients and different bioactive compounds including phenolic compounds, vitamins, minerals, and fibers. Many dietary compounds, present in fruits, vegetables and spices have been isolated and evaluated for their therapeutic potential. Evidence suggests that the health benefits of fruits and vegetables are attributed to the interactions of the phytochemicals present in whole foods by modulating several metabolism pathways. The most well-known compounds are health-promoting effects emerged because their consumption was related to a reduced incidence of cancer, cardiovascular, neurodegenerative, and age-related diseases (21).

The liver plays a central role in the metabolism of BL. It is responsible for their capture, storage, conjugation and excretion. The BNC circulate in plasma in a complex bound to AIB (BL + AIB) and enters the hepatocyte by a surface sinusoidal (figure 1).

After hepatic apical and subapical, BL may remain in the liver cells (storage) connected to cytoplasmic proteins. It can also be moved into the smooth endoplasmic reticulum of the hepatocyte and undergo conjugation with one or two molecules of glucuronic acid (UDP-glucuronosyltransferase (UGT) by the cytoplasmic enzymes of the UGT1A family). In the cytoplasm, the glucuronide compounds can be transported into the canaliculi by the canalicular organic anion transporting polypeptide (OATP1B1) and OATP1B3, which are responsible for the excretion of bilirubin into the bile. The BNC is then secreted into the intestine where it is excreted in the feces as bilirubin.

In human plasma there are 4 main forms of circulating BL unconjugated bilirubin (U-Bil), also known as bilirubin or indirect bilirubin (IB); monoconjugate bilirubin (bilirubin-conjugated or conjugated bilirubin (CB); unconjugated bilirubin (Bil)); also known as hepatic graft power coherently bound to albumin, respectively. Another BL fraction to consider is the free BL that is not bound to albumin. BL is transported in plasma bound to AIB with a high affinity for the AIB primary binding site. The free BL can be associated with different toxins. This free fraction is the one that is lost when measuring the total serum bilirubin levels.

Bilirubin is an active.player in the gut microbiome, where it can be converted into other metabolites that can be absorbed and transported to the liver. This process is regulated by the expression of bacterial genes and can be influenced by diet and lifestyle factors. The intestinal bacteria can also influence the absorption of drugs that are conjugated to bilirubin, which can affect their efficacy and safety.

In conclusion, the concentration of BL is influenced by several factors, including dietary intake, genetic factors, and gut microbiome. The role of diet in the regulation of bilirubin levels is an emerging area of research, and further studies are needed to better understand the mechanisms involved.

Table 2: Some of the dietary compounds that modify bilirubin concentrations (contd. from table 1)

<table>
<thead>
<tr>
<th>Name</th>
<th>Type of Substrate</th>
<th>Type of Modification</th>
<th>Genotypes</th>
<th>Function</th>
<th>Clinical Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peppermint oil</td>
<td>Alcoholic beverages</td>
<td>Alkyl glucuronide conjugation</td>
<td>UGT1A1*28</td>
<td>Inhibits bilirubin glucuronide conjugation</td>
<td>Decreases bilirubin levels in the plasma</td>
</tr>
<tr>
<td>Rutin</td>
<td>Alcoholic beverages</td>
<td>Alkyl glucuronide conjugation</td>
<td>UGT1A1*28</td>
<td>Inhibits bilirubin glucuronide conjugation</td>
<td>Decreases bilirubin levels in the plasma</td>
</tr>
<tr>
<td>Epicatechin</td>
<td>Alcoholic beverages</td>
<td>Alkyl glucuronide conjugation</td>
<td>UGT1A1*28</td>
<td>Inhibits bilirubin glucuronide conjugation</td>
<td>Decreases bilirubin levels in the plasma</td>
</tr>
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REFERENCES