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I Encontro Nacional de Estudantes

28 a 30 de outubro 2016

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Dietary compounds that modify Bilirubin levels

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Abstract

Bilirubin (BL) is a bile pigment that arises from the catabolism of hemeproteins and it is an important biochemical marker for diagnosis and monitoring of hepatic and hematologic diseases. The high concentration of this metabolite in plasma may be associated with disturbances in production, metabolism and/or excretion. Several *in vivo* and in *vitro* studies established the antioxidant, anti-inflammatory and anti- tumoral properties of bilirubin. Clinical and prospective studies show that slightly elevated serum bilirubin levels are positively correlated with a lower prevalence of oxidative stress-mediated diseases. In this review, detailed information on dietary compounds related to changes in serum bilirubin levels are provided. Most of the reviewed articles described compounds that inhibit or induce the most important enzymes in BL metabolism. Knowing how to modulate bilirubin levels by these compounds would be useful as a therapeutic approach, either to lowering serum bilirubin levels, in cases of hyperbilirubinemia, or to increase bilirubin concentration in order protect against oxidative stress. Several studies refer four botanical groups as associated to changes in bilirubin concentrations: Cruciferae (e.g., broccoli), Rutaceae (citrus), Liliaceae (e.g., onions), and Leguminosae (legumes).

Key words: bilirubin levels, hyperbilirubinemia, oxidative stress prevention, dietary compounds.

Introduction

Bilirubin (BL) is a yellow-orange pigment resulting from the catabolism of hemeproteins(1). This tetrapirrolic metabolite belongs to one of the most conserved superfamily of molecules in living organisms. BL has been subject of study for more than three centuries by chemists, biochemists, biologists and researchers from many fields. In clinical diagnosis, BL is a marker of liver function and used to monitoring hematological diseases(2). In the general population, there are several factors known to influence serum bilirubin levels (SBL), including genetic (3–5) and non-genetic variables (6).

The enzyme that catalyzes BL conjugation is the hepatic uridine diphosphate glucuronyl transferase 1A1 (UGT1A1). Unconjugated BL (UCB) is a lipid soluble molecule but after conjugation (with one or two molecules of glucuronic acid) becomes water soluble (conjugated bilirubin: CB), allowing its excretion via the bile canaliculi. The most prevalent metabolic disorder in the Caucasian population is Gilbert's Syndrome (GS). It´s a benign condition, characterized by moderate hyperbilirubinemia in the absence of hemolysis or liver dysfunction(3). The common variant associated with this syndrome is the TA duplication at position c.-41_-40dupTA (variant UGT1A1*28 or A(TA)7TAA allele) located in the promoter region of the UGT1A1 gene(3). The presence of hyperbilirubinemia, associated with GS, can lead to the worsening of clinical symptoms of individuals with chronic hemolytic diseases (7). Moreover, patients with GS are more sensitive to the adverse effects of antineoplastic drugs and others suffering hepatic glucuronidation, whereby the diagnosis gains importance in terms of treatment of many disorders(8).

At high concentrations, as described in children with Crigler-Najjar syndrome type I (SCN-I) or type II (SCN-II), BL can be extremely toxic. For many years, the bile pigment bilirubin was considered to be a cytotoxic lipid-soluble waste product formed during heme catabolism. Since the early nineties, several biochemical and clinical studies suggests that bilirubin acts as a potent physiologic antioxidant that may provide important protection against stress related disorders (9–11).

Most of the work undertaken to understand the potential protective effect of BL focuses on BL protection mechanisms in atherosclerosis (12). Atherosclerosis is an inflammatory process in which lipid deposition on the arterial wall results from high levels of circulating cholesterol, a stage in the early injury. BL, as an antioxidant, reduces the formation of oxidized low density lipoprotein (LDL), also an important step to initiate this process (13,14), inhibits chemotaxis of monocytes and attenuates the expression of adhesion molecules on endothelial cells (15).

The properties of BL as an antioxidant were confirmed in the animal model, the Gunn rat, which has an autosomal recessive deficiency of the enzyme UGT1A1. Homozygous rats present hyperbilirubinemia and heterozygous have normal levels of BL (16). The use of this animal model showed that serum bilirubin exerted a protective effect against oxidative damage during the neonatal period when they were exposed to hypoxia and neonatal jaundice (17).

Another protective effect of BL is related to its anti-carcinogenic activity (18), as verified in caco cells and HepG2 cells, where the addition of tetrapirrolic compounds, such as protoporphyrin, urobilin or estercobilin has induced DNA damage and apoptosis of tumor cells (18). These observations have encouraged researchers to conduct numerous epidemiological and experimental studies to clarify the mechanisms involved in its potential protective effect.

Certain dietary compounds may increase or decrease BL levels. It is well known that drugs and other substances that can compete with BL for glucuronidation also contribute to the raising of SBL(19). Some herbal extracts can even exert inhibitory effects of UGT1A1 activity and thereby increase BL levels (19). On the other hand, there are dietary components that increase enzymatic activity of UGT1A1 , such as citrus fruit(20) and some constituents of Cruciferous vegetables (eg. cabbage and broccoli) (21) by increasing the expression of UGT1A1 gene. In animal models it was demonstrated that soy protein and soy isoflavones enhance hepatic UGT activity (22)and the allyl sulfides onion and garlic also had the same effect on different enzymes of the UGT family (20). These interactions must be recognized as a possibility to modulate bilirubin levels in different situations. On one hand the management of the most important clinical entity, the hyperbilirubinemia by diminuishing (decreasing) SBL and in contrary (on the other hand – para ser coerente), raising SBL to prevent stress related diseases.

Revision

Brief description of bilirubin metabolism

In human plasma there are 4 main forms of circulating BL: unconjugated bilirubin (UCB, also known as indirect bilirubin – IB); conjugated bilirubin (CB, or direct bilirubin); bilirubin covalently bound to albumin (Alb); free BL that is not bound to albumin (23). The free BL presents a very low nanomolar concentration increase when BL exceeds the molar concentration of Alb, saturating his binding site (24). The binding of BL to ALB increases with postnatal age but is reduced in the presence of certain drugs (25). The free BL correlates better with BL toxicity than any other fraction.

The main source of BL is the heme group of hemoglobin from the destruction of senescent erythrocytes, which contributes around 80-85% of total production(1). The remaining 15 to 20% of BL production results from the turnover of other liver hemeproteins such as myoglobin, catalase and cytochrome (1). A small proportion (1-5%) results from the premature destruction of premature erythrocytes in bone marrow or spleen. In normal adult, approximately 250-300 mg of BL is produced per day, equivalent at 3.8 mg/kg (26).

Under physiological conditions, the majority of normal erythrocytes are removed from the circulation after 120 days of life and they enter into the reticuloendothelial system. The heme catabolism, resulting in BL production, occurs within macrophages of the spleen, bone marrow and in Kupffer cells. After the heme breakdown BL is released into the plasma (1). In this mechanism, the ring of ferroprotoporfirina IX heme group, the prosthetic group of proteins such as hemoglobin, myoglobin and cytochrome P-450, suffers the catalytic action of heme oxygenase (HO-1). This enzyme consumes three molecules of oxygen and requires a reducing agent, nicotinamide adenine dinucleotide phosphate (NADPH). The enzyme HO-1 acts at the central bridge methionine, forming biliverdin (BLV) (27) and is located in the plasma membrane of the endoplasmic reticulum, nucleus and mitochondria (27). The activity of this enzyme is rate limiting step in heme catabolism and BL production(28). Its synthesis is induced by stimuli associated with oxidative stress, including free oxygen and bacterial lipopolysaccharide radicals (29) by increasing the intracellular concentration

of hepatic heme induced by various drugs, natural compounds, cytokines and growth factors (29). From the oxidation of heme also results iron (Fe2+), carbon monoxide (CO) and BLV. The BLV is, in turn reduced to BL in a reaction that is catalyzed by biliverdin reductase (BVR), dependent on NADPH (30). At this stage, BL is called UCB and circulates in the blood bound to albumin (Alb). Alb greatly enhances their solubility due to two binding sites for this molecule and also prevents its excretion into urine. In healthy individuals, about 99.9% of BL circulates in complex with albumin as CB (27).

The liver plays a central role in the metabolism of BL. It is responsible for their capture, storage, conjugation and excretion (31). As already mentioned, the BNC circulates in plasma in a complex bound to Alb (BL- Alb) entering the hepatocyte by its sinusoidal surface (figure 1). The complex passes through the thin and discontinuous cells, with pores, that contour the endothelial sinusoidal and reach the space of Disse, which has direct contact with the sinusoidal basolateral surface of liver cells (32).

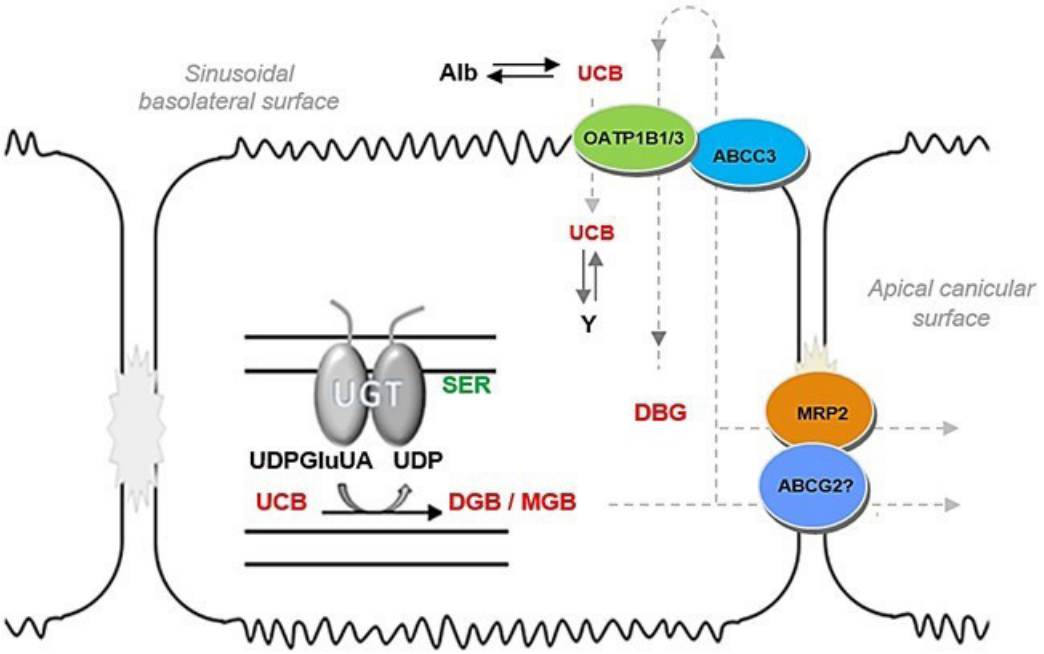

Figure 1 – Bilirubin hepatic uptake, conjugation and glucoronid transporters.

SER: smooth endoplasmic reticulum; UCB: unconjugated bilirubin; Alb: albumin; MGB e DGB: mono and diglucuronid; Y: ligandin; UGT1A1: uridine 5'-diphospho-glucuronosyltransferase 1A1 (UDP-glucuronosyltransferase, UGT); UDPGlcUA: glucuronic acid residue; OATP1B1/3: organic anion transporter, 1B1 and 1B3; ABCC3: ATP-Binding Cassette transporter, (Sub-Family C, CFTR/MRP, Member 3); MRP2: Multidrug Resistance-associated Protein 2; ABCC2: ATP-Binding Cassette transporter (sub-family G member 2). The image also shows the location of UGT1A1 in the membrane of smooth endoplasmic reticulum membrane (SER); transport of unconjugated bilirubin (UCB) into hepatocyte at the sinusoidal surface by the action of the organic anion basolateral transporters OATP1B1/3 (organic anion transporter, 1B1 and 1B3); ligandin assembles and transport UCB to the SER; conjugation of UCB by UGT1A1 results in bilirubin glucuronides (MGB, DGB); glucuronides are water soluble and are transported to the exterior of the hepatocyte, at the apical canaliculi surface, by the MRP2 (Multidrug Resistance-Associated Protein 2) and ABCC2 (ATP-Binding Cassette transporter - sub-family G member 2), and possibly by the ligandin (initially named Y protein) a glutathione-S-transferases (32), which despite being in much smaller quantity, can pass through the protein ABCC3 a ATP-Binding Cassette transporter, (Sub-Family C, CFTR/MRP, Member 3) and be again captured by OATP transporters.

After hepatic uptake and metabolism, BL may remain in the liver cells (storage) connected to cytoplasmic proteins. It can also move to the smooth endoplasmic reticulum of the hepatocyte and undergo conjugation with one or two residues of glucuronic acid (UDPGlcUA) by the catalytic action of UGT1A1 forming monoglucuronide (MGB) or diglucuronide (DGB), named as conjugated bilirubin (CB). In the gut this CB undergoes oxidation by the action of intestinal enzymes and bacterial flora and urobilinogen is formed as other pigments. The Urobilinogen may again be captured to the liver (enterohepatic circulation) and may be conjugated (33).

The SBL reflect the hemoglobin catabolism as a result of destruction of erythrocytes or the ability of hepatocytes

to process bilirubin (absorption, storage and conjugation) or the functioning of the biliary system that transfers the bile to the duodenum.

Disease Risk and bilirubin protection

Some studies point out that UCB may prevent cardiovascular disease (CVD) and other chronic diseases. Clinical evidence indicates that hyperbilirubinaemic 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 (34,35) and the respective causes or co-morbidities such as, type 2 diabetes (36), metabolic syndrome, hypertension (37), chronic kidney disease (38)and albuminuria (39). It was observed the same association, as described above, with other disease conditions which physiopathology is related to oxidative stress, such as rheumatoid arthritis(40), multiple sclerosis (41), cancer (42,43) and overall mortality (42). Similarly, the analysis of the association between SBL and risk factors for these chronic diseases, such as lipid profile (35), anthropometric index (44) and C-reactive protein (45) was also performed in several studies.

Acquired factors that modulate Serum bilirubin levels

It has been shown that there is a significant difference in plasma levels of BL (SPB) between men and women and between different age groups (46). The differences between gender have been attributed to hormonal differences (46), in particular, because testosterone decreases the activity of UGT1A1 and estrogens and/or progestogens increase the activity of the same (47). The effect of testosterone may however, explain that GS, a hereditary hyperbilirubinemia, is more often detected in males during puberty than in females, and also explain the difference in accordance with age (47). It is believed that gender differences may be due to the fact that men have higher cell mass or greater turnover of the hemoglobin (48).

BL levels reach a maximum between 19 and 24 years old individuals, decreasing continuously throughout life (48,49). But it is in the neonatal period where significant variations of BL levels are observed. Virtually all infants have higher levels of BL in the first days of life (50). There is a significant difference in ethnicity between NPB. One of the first studies conducted to evaluate these differences was conducted on a sample of 1,538 Americans. The study revealed that African-Americans have lower levels of BL than Latinos, Asians and Caucasians of European origin (51) in addition to these racial differences the differences are more pronounced among women than among men (51). Genetic factors greatly contribute for inter-racial differences, since there are differences in gene frequencies.

It is described that smokers have lower SBL than non-smokers (52,53). Recently, it was also revealed that the cessation of smoking is followed by an increase in the concentration fractions of all BL (53). Studies reveled that BL is inversely associated with the duration of tobacco exposure and the amount of cigarettes smoked per day (54). The relationship between alcohol consumption and SBL is controversial, since there are studies that indicate that BL increases with alcohol consumption (55,56) and others describe no clear association with this factor (57).

Dietary compounds and bilirubin levels

An extensive variety of fruits and vegetables offer a range of nutrients and different bioactive compounds including phytochemicals, 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 metabolic pathways. The impression that these compounds have health promoting effects emerged because their consumption was related to a reduced incidence of cancer, cardiovascular, neurological, respiratory, and age related diseases (58–61). However, the molecular mechanism by which food-derived compounds exert their beneficial effects remains poorly understood due to the complexity of related pathways. The clinical importance of controlling elevated SBL(hyperbilirubinemia) and in other hand the possible beneficial effects of BL mildly elevated levels on chronic diseases (potential protective effect of BL) suggests the search for strategies to modulate SBL. This strategies may include administration of drugs or dietary compounds which can increase or decrease the efficiency of hepatic bilirubin conjugation by UGT1A1 enzyme, administration of HO-1 or BLVR inducers (to produce more BL) and rise tetrapirroles by supplementation with BL or BLV or similar compounds from other sources. Some studies cited in this article did not aim directly to perceive the interference of certain dietary compounds in the SBL. However, their results were analyzed because in some way the observations are associated with changes in BL production or excretion. Firstly we will summarize inducers and inhibitors of UGT genes, the superfamily where the gene that encodes UGT1A1 belongs to.

The UGT superfamily is divided into UGT1 and UGT2 families; both are a phase II biometabolizing enzymes.

TheUGT1A subfamily, is in charge for the glucuronidation of endogenous compounds such as bilirubin (62), as well as phenols, anthraquinones, and flavones(62), sex steroids, 17β-estradiol (eg. estrogen) and estriol (63) and cooked-food carcinogens(64). From the nine proteins that belongs to this subfamily the UGT1A1 is responsible for BL conjugation(8). In the UGT1 family the presence of genetic variants can alter considerably their clearance efficacy.Variants of the UGT1A1 gene that decrease UGT1A1 enzyme activity can lead to jaundice as seen in Gilbert's syndrome or in Crigler-Najjar syndrome. As already mentioned, the most important genetic variant responsible for the SBL variation observed in Caucasian population is the repeat polymorphism in the TATA box region of the UGT1A1 promoter. This allele variant consists of seven thymine adenine (TA) repeats, in the A(TA)nTAA motif (allele 7), while the common allele is characterized by the presence of six TA repeats (allele 6). Homozygous individuals carrying the 7/7 genotype had higher levels of unconjugated bilirubin caused by a reduction of 30% in UGT1A1 transcription (65).

Recent published works try to analyze the impact of several dietary compounds in UGT1A1 activity using serum bilirubin as an endogenous marker of enzyme activity. They also take in account the genotype for the TA promotor polymorphism of the participants in order to analyze the genetic-environmental interaction (20,21,66).Four ofthese studies, performed by the same group of researchers, investigated whether food from different botanical groups were associated with changes in UGT1A1activity. Most of the tested food were cruciferous, soy and citrus, all sources of UGT inducers (67). Table 1 shows the resume of these works and others that described changes in SBL.

Table 1 – Sources or dietary compounds that potentially modulate serum bilirubin levels.

Dietary compounds or dietary sources intake	Type of study	Effect on bilirubin levels Summary	Reference
Record of food intake from four botanical groups: Cruciferae, Rutaceae, Liliaceae and Leguminosae.	Observational	Decreased. Only homozygotes 7/7 showed decreased bilirubin concentrations after consuming cruciferous vegetables but not with the intake of other investigated botanical groups.	(21)
Cruciferous, citrus and soy (doses adjusted for body weight)	Clinical	Decreased. The intake of cruciferous vegetables, soy foods and citrus fruit seems was associated to a decrease on SBL but only in women that are homozygous 7/7.	(66)
Record of food intake Citrus fruit, cruciferous and soy	Observational	Decreased. Women homozygous 7/7 that consume citrus fruit may exhibit a higher activity of this gene than those who do not include it on their diet.	(20)
Cruciferous, citrus and soy (Different quantities of Cruciferous supplementation)	Clinical	Decreased within all of three group of vegetable and it was observed in the three genotypes. Results suggest a dose-response.	(68)
Soy	In vivo	Decreased	
Resveratrol (Resveratrol doses)	Clinical	Decreased. UGT1A1 activities were minimally affected by the intervention. Is more pronounced in individuals with low baseline enzyme activity.	(69)
Dandelion	In vivo	Decreased	(70)
Rooibos	In vivo	Decreased	(71)
Honeybush tea	In vivo	Decreased	(71)
Rosemery	In vivo	Decreased	(71)
Ellagic acid	In vivo	Decreased	(71)
Ferulic acid	In vivo	Decreased	(71)
Curcumin	In vivo	Decreased	(71)
Astaxanthin	In vivo	Decreased	(71)
Green tea	In vitro	Increased	(71)
Rutin	In vitro	Increased	(71)
Naringenin	In vitro	Increased	(71)
Allspice	In vitro	Increased	(71)
Peppermint oil	In vitro	Increased	(71)
Cacao	In vitro	Increased	(71)
Quercetin (polyphenolic)	In vivo / In vitro	Increased	(71)
Carnosol	In vitro	Increased	(71)

Discussion

Peterson and colleges (21), performed an observational study (using food records) to analyze the association between the four botanical groups: Cruciferae, Rutaceae, Liliaceae, and Leguminosae (all sources of UGT inducers) and bilirubin concentrations. Results showed an interaction between UGT1A1 genotype and Cruciferous intake. Individuals with the 7/7 genotype with increased intake of cruciferous vegetables had lower SBL. One explanation given by the authors for this results is that individuals with 7/7 genotype had elevated BL concentration and the ability to detect differences in the serum of these participants is greater. Intake of food from the other three botanical groups showed no association with SBL.

Another study, a randomized, controlled, fruit and vegetable feeding trial (66) with doses adjusted for body weight, showed that the intake of cruciferous vegetables, soy foods and citrus was associated with a decrease in SBL, but it was only observed in women that were homozygous 7/7.

The third work, based on food record showed that citrus fruit intake elevated the activity of UGT1A1 gene among individuals that included it on their diet. But this was only observed in women homozygous for allele 7 too.

In a controlled feeding study with a mixed diet of cruciferous, soy and citrus (68) researchers tested different dosages relatively to a basal diet. The results showed that SBL decreased in response to all three vegetables-containing diets comparing to the fruit –and vegetable-free basal diet. This results were also more pronounced among individuals with 7/7 genotype, however, it was also possible to observe the same association among other genotypes.

In a study performed to evaluate the ability of soy to induce phase II detoxification enzymes, the researchers concluded that dietary soy enhances the enzyme activity, especially quinone reductase and UGT1A enzymes, which could lead to protection from potentially harmful xenobiotics (69). At the same time UCB will also have to induce this group of enzymes, including dandelion, rooibos tea, honeybush tea, rosemary, ellagic acid (present in berryes, pomegranate, grapes, walnuts, and blackcurrants), ferulic acid, curcumin (major active component of the food flavor turmeric and curcumin) , and astaxanthin, to enhance UGT activity and therefore diminishing SBL (table 1). In contrast, there are some dietary compounds like polyphenols epicatechin and chrysin that can inhibit UGTs (72). Among other food components that have the same effect on UGTs enzymes are green tea, quercetin (natural polyphenol flavonoid: 3, 3, 4, 5, 7-pentahydroxyflavone that is abundant in various fruits and vegetables and stimulates antioxidant and anti-inflammatory activities), rutin glycoside between the flavonol quercetin and the disaccharide rutinose), naringenin, allspice, peppermint oil and cacao (73).

As already described above, HO-1 catalysis heme degradation producing CO, which has anti-inflammatory properties; biliverdin that is converted to bilirubin by BVR that also has a powerful antioxidant capability; and free iron bound to the heavy chain ferritin (H-ferritin), another antioxidant molecule. HO-1 has been suggested to be an important therapeutic target in various disease (29,74). The fact that HO -1 represents the rate limiting enzyme of BL production, elevating the expression of HO-1 could lead to more BL production. This enzyme is inducible by numerous agents which promote oxidative stress, and is now known to provide important antioxidant protection, as demonstrated in animal models and epidemiologic studies. One of the most studied phytochemical that induces HO-1 activity is quercetin which, as already described above, is a polyphenolic compound that also increases BL concentration. In a recent study, the authors reported the results offsetting 56 compounds on the up-regulation of protein HO-1 in microglia cells in vitro. The compounds were selected over more than 100 and their HO-1 stimulating capacity with their effect on cell viability was analyzed. They selected 10 positives (including hemin) and 5 negatives to further examine their effect on heme metabolism and modulation of the inflammatory response. They carnosic acid, carnosol, cobalt protoporphyrin IX, dimethyl fumarateand supercurcumin as the compounds causing the greatest HO-1 induction and low cytotoxicity. They also distinguished between those compounds capable of promoting the generation of HO-1-derived products (bilirubin)namely the dietary compounds carnasol, supercurcumin and others that do not, indicating that HO-1 induction may be independent of heme-degradation metabolism.

Curcumin can also induce this cytoprotective enzyme. It is extracted from dry rhizome of Curcuma longa Linn (Zingiberacee). This herb is widely cultivated in tropical regions of Asia. It has been used for centuries in indigenous medicine for the treatment of a variety of inflammatory conditions and other diseases. Several studies in recent years have shown that curcumin is a potent inhibitor of tumor initiation in vivo and (75) and possesses antiproliferative activities against tumor cells (76). Although, the exact mechanisms by which curcumin promotes these effects remains to be elucidated. It has been shown in vivo that this compound enhances the activities of detoxifying enzymes such as UGT but it also induces a distinct antioxidant genes such us HO-1 in mammalian tissues contributing to the variety of pharmacological actions mediated. These facts could seem contradictory but the inducing HO-1 could not result in more bilirubin production, it could be an independent induction of heme degradation pathway. In the process of

scavenging physiological oxidants by electron donation BL is often reconverted to BLV and the enzyme BLVR quickly regenerates BL. This seems to be the reason why BL is an effective antioxidant. However, the exact mechanism underlying this system remains largely undefined (77).

Inducing or inhibiting BLVR would lead to changes on BL regeneration about food components that may alter BLVR. We didn´t find any information. An hypothesis suggested by McCarty (78) to raise tissue or serum BL could be oral administration of BL or the more soluble BLV. The same author reviewed several experimental studies that demonstrate the anti-inflammatory properties of BLV when it was administrated in rodents (79). Other authors propose that supplementation with nutraceuticals containing plant tetrapyrolles, such as phycocyanobilins (80), or their improved consumption in the form of natural foods (81) might be used as a novel method of the chemoprevention of obesity, metabolic syndrome, and diabetes.

Conclusion

From all that was exposed in this review about BL metabolism and considering all genetic and acquired factors that can affect his serum concentration, it is obvious that modulating SBL, by means of dietary compounds, would be a challenge.In a hyperbilirubinemiastate, where it is important to decrease serum bilirubin levels, the best approach would include the increasing UGT1A1 expression and this can be achieved with foods from the different botanical families Cruciferae (e.g., broccoli), Rutaceae (citrus) and Liliaceae (e.g., onions).

Regulation of UGTs by phytochemicals has been investigated with a focus on cancer prevention and numerous inhibitors from plant origin (epicatechin gallate, epigallocatechin gallate, octyl gallate, propyl gallate, quercetin, tannic acid, benzoin gum, capsaicin, dihydrocapsaicin, eugenol, gallocatechin gallate, geraniol, menthol, menthyl acetate, naringenin, allspice berry oil, N-vanillylnonanamide, clovebud oil, peppermint oil, silibinin, and silymarin).

The results presented in this review demonstrate that that some beneficial effects of curcumin might take place because of the intrinsic ability of this yellow pigment to increase HO-1 and possibly other intracellular protective pathways.

The strategy to rise SBL in order to fight oxidative stress by inhibiting UGT1A1 activity appears to be unreasonable because UGT1A1 also glucuronides estrogens and several dietary carcinogens. The enzymes HO-1 and BLV would also have an important role in the development of therapeutic strategies based on dietary compounds to prevent stress related diseases by elevating SBL; however, for these two enzymes there was considerable less information about their inducers and inhibitors. Additional studies are needed to stablish the compounds that best modulate SBL and the molecular mechanisms involved.

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