BRONCHIAL ASTHMA AND BILIRUBIN

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Abstract. Currently, data are accumulating on the antioxidant properties of bilirubin and its protective role in various diseases. This review considers the dose-dependent effect of bilirubin on its cytoprotective and antioxidant properties, the relationship between the level of bilirubin and the pathophysiological manifestations of bronchial asthma, in the pathogenesis of which chronic inflammation induced by oxidative stress plays a significant role. The article also focuses on the potential therapeutic use of bilirubin in the treatment of bronchial asthma.

Keywords: bilirubin, heme oxygenase-1, bronchial asthma.

List of Abbreviations

BA – Bronchial asthma
OS – Oxidative stress
FRP – Free radical processes
AOA – Antioxidant activity
ROS – Reactive oxygen species
PPARa – Peroxisome Proliferator Activated Receptor Alpha
FABP1 – Fatty Acid-Binding Protein 1
HO-1 – Hemoxygenase-1
CO – Carbon monoxide
NLRP 3 – Nod-like receptor family pyrin domain-containing protein 3
5-LOX – 5-lipoxygenase
BRNPs – Bilirubin nanoparticles

Bronchial asthma (BA) is characterized by variable limitation of expiratory air flow. Recurrent episodes of bronchial obstruction in asthma have been associated with chronic airway inflammation (Reddel *et al.*, 2022). A key role in the initiation and activation of the inflammatory process in BA is played by oxidative stress (OS), which is characterized by increased free radical processes (FRP) with insufficient activity of antioxidant defense (AOA) (Michaeloudes *et al.*, 2022; Nadeem *et al.*, 2014; Lewis *et al.*, 2014).

The respiratory tract, which represents the body's first line of defense against the effects of atmospheric pollutants, contains a large number of both enzymatic and non-enzymatic antioxidant systems (Sackesen *et al.*, 2008). Various low molecular weight substances can act as non-enzymatic antioxidants.

Bilirubin is one of the endogenous low molecular weight metabolites with an antioxidant effect (Vitek *et al.*, 2023). Bilirubin has long been considered a nonfunctional waste product of heme catabolism. An increase in its content in the body was previously traditionally regarded as a negative phenomenon and was interpreted either as a manifestation of pathology (in diseases of the liver and biliary tract), or as

a potentially dangerous factor (in "kernicterus" caused by Rh incompatibility of mother and child) due to the cytotoxic effect on many tissues (Vitek *et al.*, 2023).

However, in recent years, there have been more and more studies showing the possible protective effect of bilirubin in a number of pathological conditions (Vitek, 2017; Wagner *et al.*, 2015).

Bilirubin exchange

Bilirubin is a bright yellow pigment that is an important metabolite (conversion product) of heme and is formed during hemolysis of old and defective red blood cells in macrophages of the spleen and liver. A small amount of bilirubin is also formed by macrophages of the red bone marrow, which absorb the defective red blood cells formed there with ineffective erythropoiesis.

There are two fractions of bilirubin depending on their physicochemical properties. The predominant form of bilirubin that circulates in the blood serum is indirect or free bilirubin. The combination of bilirubin with highly polarizing glucuronic acid makes it soluble in water, which ensures its transfer to bile and filtration in the kidneys. This form is called conjugated, bound, or direct bilirubin.

Currently, as a result of the identified antioxidant properties of bilirubin, data on its protective effect on a number of diseases are accumulating (Vitek *et al.*, 2023; Vitek, 2017; Wagner *et al.*, 2015; Stocker *et al.*, 1987). The antioxidant properties of bilirubin are based on its structure. Bilirubin includes 4 pyrrole rings and contains an extended system of conjugated double bonds and an active hydrogen atom. This metabolite can combine with the lone pair of electrons of oxygen radicals and, by absorbing the formed ROS, prevent oxidation. One molecule of bilirubin can break off more than two oxidation chains due to the formation of conversion products with inhibitory properties, and can protect cells from a 10,000-fold excess of H2O2 (Stocker *et al.*, 1987; Baranano *et al.*, 2002).

The antioxidant and protective properties of bilirubin are also determined by its concentration in biological media. Its optimal level in blood serum is currently the subject of debate. The physiological range of serum bilirubin is conventionally defined as 5–17 μmol/L. However, serum concentrations of this metabolite below 10 μmol/L are associated with a higher risk of various diseases, which further increases when the concentration decreases to 5-7 μmol/L. It may be necessary to establish the health risks of these lower serum bilirubin concentrations, despite the fact that they are within the physiological range (Vitek*et al.*, 2023; Creeden *et al.*, 2021). Thus, Creeden *et al.* proposed cut-off values for normobilirubinemia ranging from 10 to 25 μmol/L depending on age, sex, and race, and for hypobilirubinemia <10 μmol/L (Creeden *et al.*, 2021). On the other hand, the negative impact on health may be associated somewhat with its own low concentration of bilirubin, as much as with exposure to infectious agents capable of reducing the concentration of bilirubin in the blood serum. Thus, it is known that H. pylori infection is an independent risk factor for a decrease in serum bilirubin concentration and a less favorable lipid profile (Zhao *et al.*, 2019).

It is also known that the concentration of bilirubin in the blood serum in women is lower than in men, which may be due to a lower number of red blood cells in women, as well as the influence of estrogens and androgens (Scherbinina, 2007; Muraca & Fevery, 1984).

At the same time, abnormal and slightly elevated concentrations of bilirubin in the blood serum can protect against oxidative stress, contribute to the suppression of autoimmune and degenerative processes, and correct metabolic disorders. In addition, bilirubin has been shown to participate differently in the regulation of signaling pathways, depending on concentration, by binding to nuclear receptors (Peroxisome Proliferator Activated Receptor Alpha, PPARa) (Creeden *et al.*, 2021).

Currently, at least two direct targets of the bilirubin receptor have been identified: one at physiological levels (nuclear transcription factors PPARa), and the other at higher pathological concentrations causing an intracellular calcium signaling response (Vitek*et al.*, 2023).

It is worth noting that specific nuclear PPAR receptors are currently considered as the main regulators of both cellular and energy homeostasis of the whole organism (Hong *et al.*, 2019). Thus, it is likely that normal bilirubin levels are indirectly involved in the regulation of the body's energy state.

Perhaps the intracellular concentration of bilirubin is more important. For example, 7 ng/mg bilirubin acts as an antioxidant, while intracellular concentrations above 25 ng/mg are associated with pro-oxidant and cytotoxic effects (Bianco *et al.*, 2020). Bianco A. *et al.* showed that intracellular bilirubin concentrations varied significantly among hepatocyte, neuronal, cardiac endothelial, and tubular epithelial cell lines, with the highest intracellular bilirubin concentration observed in neuronal cells and the lowest in hepatocytes (Bianco *et al.*, 2020). The authors also determined the threshold of intracellular concentration acceptable for various cell types which determines the switching between the antioxidant and prooxidant effects of bilirubin (Bianco *et al.*, 2020). The vulnerability of neurons may be associated with lower activity of mitochondrial enzymes that oxidize bilirubin, as well as reduced expression of bilirubin transporters across the cell membrane, which normally limit the intracellular accumulation of pigment. It should be noted that bilirubin enters cells either through a specific carrier molecule or through passive diffusion. The contribution of each mechanism depends on the concentration of bilirubin (Mediavill *et al.*, 1999). It is important to note that intracellular bilirubin is capable of binding to Fatty Acid-Binding Protein 1 (FABP1) (Levi *et al.*, 1969). FABP has been proven to target fatty acids or other hydrophobic agonists (bilirubin) on nuclear transcription factors PPAR (PPAR-α, PPAR-δ and PPAR-γ) (Tan *et al.*, 2002).

The role of enzyme systems in the production of bilirubin

Bilirubin production is associated with one of the enzymatic antioxidants, the hemooxygenase-1 (HO-1) system. A number of authors believe that HO-1 plays a crucial protective role in the lungs against OS (Ryter, 2022). Hemoxygenase-1 (HO-1) is the main enzyme that decomposers heme into free iron (Fe2+), biliverdin and carbon monoxide (CO). This enzyme reduces bileverdin to bilirubin and physiologically regenerates bilirubin in the catalytic cycle, providing antioxidant cytoprotection. The enhancement provided by this cycle may explain the ability of low nanomolar concentrations of bilirubin to overcome 10,000 times higher concentrations of oxidants.

Perhaps, bilirubin provides physiological antioxidant activity to different types of intracellular molecules. Bilirubin, which has high lipophilicity, is closely related to cell membranes, where it can prevent lipid peroxidation and protect membrane proteins (Baranano, 2002; Ryter, 2022). According to Lv J. *et al.*, heme oxygenase-1 attenuates apoptosis of airway epithelial cells and allergic airway inflammation through negative regulation of the expression of Nod-like receptor family pyrin domain-containing protein 3 (NLRP 3), a pathogen recognition receptor that forms a caspase-1 activating complex, known as the NLRP3 inflammasome (Lv *et al.*, 2018)

Heme-induced HO-1 and its products, bilirubin and CO, also eliminated RXRa/β/γ-mediated apoptosis of epithelial cells of the respiratory tract by binding RXRa/β/γ (nuclear retinoid receptors) in a manner independent of enzymatic activity (Lv *et al.*, 2018).

It should be noted that the product of heme oxygenase-1, bilirubin, stabilizes mitochondrial membranes. Specific doses of bilirubin can be considered as a mitochondria-targeted drug against inflammasome-related diseases (Li *et al.*, 2022). Suppression of inflammasome activation is carried out both by hemeoxygenase-1 directly and by its product, bilirubin.

It has been shown that genetically reduced hemoxygenase 1 activity (encoded by the HMG1 gene), leading to a decrease in bilirubin levels, was associated with impaired respiratory function and a higher risk of developing respiratory diseases (Fredenburgh, 2007).

Polymorphisms of the HMOX1 gene affecting the expression of HO-1 contribute to the development of new-onset bronchial asthma in

children, while the S allele of HMOX-1 has a protective effect in asthma (Li *et al.*, 2022). It is possible that heme oxygenase 1 polymorphisms can alter the production of not only bilirubin, but also other metabolites that affect respiratory function.

Bilirubin and asthma

A number of studies have demonstrated the role of serum bilirubin in protecting respiratory tissues from environmental stressors (Shapira, 2021; Ryter *et al.*, 2007). In the study Turi *et al.*, higher bilirubin concentrations within the normal physiological range have been shown to be associated with protection against the development of childhood asthma (Turi *et al.*, 2021). The authors suggested that the relationship between bilirubin levels and the risk of developing asthma follows a parabolic relationship, with moderately low and extremely high bilirubin levels causing an increased risk of developing asthma. However, the pathogenetic mechanisms associated with bilirubin levels and the reduction in the risk of developing bronchial asthma are not clear. Perhaps the protective effect of bilirubin is due to the fact that unconjugated bilirubin inhibits many members of the secretory phospholipase A2 (sPLA2) enzyme family (including sPLA2IIA) in a dose-dependent manner at physiologically relevant concentrations. Inhibition of sPLA2IIA in vitro is irreversible and does not depend on the concentration of the substrate. Unconjugated bilirubin is also an inhibitor of 5-lipoxygenase (5-LOX) (Jamil *et al.*, 2005; Joshi *et al.*, 2016). The above-mentioned effects of bilirubin can lead to a decrease in the production of arachidonic acid and leukotriene B4, which reduces the migration and chemotaxis of monocytes and leukocytes, as well as the production of superoxide generated by neutrophils in the respiratory tract. There was also a significant negative correlation between the levels of unconjugated bilirubin in plasma and lysophosphatidylcholine 18:2 (LPC 18:2) and lysophosphatidic acid 18:2 (LPA 18:2). sPLA2 cleave membrane phospholipids to form LPC 18:2, which are then hydrolyzed by autotaxin to form LPA 18:240 (Aoki *et al.*, 2008). These factors are activated in human bronchial lavage fluid during allergic inflammation (Georas *et al.*, 2007), contributing to airway damage, fibrosis, and increased vascular permeability (Tager *et al.*, 2008).

It should be noted that the perinatal period is characterized by the development of hyperbilirubinemia, which may have a protective value in relation to the likelihood of developing bronchial asthma in the future (Petersen & Subbarao, 2021). At the same time, low bilirubin levels are associated with the development of an "allergic march" (Jung & Hwang, 2022). According to other researchers (Kuzniewicz *et al.*, 2018), on the contrary, moderately elevated bilirubin levels in the neonatal period (9-17.9 mg/dl or 154-306 mmol/l) are associated with the development of asthma in the subsequent period. This pattern turned out to be reproducible in various populations: in Sweden, Taiwan, China, and the historical and modern cohort in the United States (Kuzniewicz *et al.*, 2018). The authors consider the most likely explanation of this phenomenon to be the presence of a distorting factor, for example, a genetic predisposition to both moderate hyperbilirubinemia and asthma, including the presence of polymorphisms in the glutathione-S-transferase gene. At the same time, more severe hyperbilirubinemia (more than 18 mg/dl) is caused by other etiological factors, such as hemolytic disease of newborns due to Rh conflict or AV0, glucose-6-phosphate dehydrogenase deficiency, sepsis. The authors also do not exclude the presence of two conflicting mechanisms of the effect of unconjugated bilirubin on the development of bronchial asthma in the future: bilirubin is both a causal and protective factor, and at a level >18 mg/dl (307 mmol/l) the protective mechanism overcomes the causal one. It was also possible that the effect on the development of asthma in the future was not hyperbilirubinemia as such, but the methods of its therapy, in particular phototherapy, however, this assumption is refuted in the study of Tham *et al.* (Tham *et al.*, 2019). These authors found no evidence of a link between phototherapy of neonatal hyperbilirubinemia and allergic sensitization.

In addition to the cytoprotective and antioxidant effects of free bilirubin, its immunosuppressive property has been shown (Jangi *et al.*, 2013). It is capable of suppressing the production of pro-inflammatory interleukins, in particular interleukin-2 (Haga *et al.*, 1996). Intracellular accumulation of free bilirubin inhibits IL-2 production by lymphocytes at concentrations of 8-12 mg/dl in a dose-dependent manner. It should be noted that inhibition of interleukin-2 production by unconjugated bilirubin can shift the T1 to T2 balance, and the predominance of the T2 phenotype is associated with the development of allergies and asthma. Higher concentrations of free bilirubin also inhibit other pro-inflammatory cytokines, including IFN-gamma and TNF-alpha (Liu, 2008). At the same time, very high levels of free bilirubin in the brain promote the release of TNF-alpha and IL-1 by astrocytes and the activation of phagocytosis in microglial cells. Thus, free bilirubin can have both an immunosuppressive effect at a physiological or moderately elevated level, and a pro-inflammatory effect at very high levels in the brain and in other organs and tissues (Silva & Vaz, 2010).

Plasma bilirubin levels may also be negatively associated with obesity, which in turn negatively affects the development and course of asthma in children (Kipp *et al.*, 2023). In a number of studies, it has been shown that in patients with asthma, as the concentration of bilirubin in blood serum increased within the normal range, the values of respiratory function increased statistically significantly (Boriskina *et al.*, 2023; Curjuric *et al.*, 2014). Thus, these results may indicate the protective role of slightly elevated bilirubin values on bronchial patency in adolescents with asthma.

In addition, bilirubin levels are positively associated with muscle mass, as demonstrated in patients with sarcopenia (Wang *et al.*, 2021). It is also possible that bilirubin may improve physical performance (Flack *et al.*, 2023). An increase in muscle mass and physical performance should undoubtedly improve the biomechanics of the act of breathing.

Therapeutic potential of bilirubin-based medicines

Taking into account the revealed protective properties of bilirubin in upper-normal values on the respiratory system, in recent years there has been interest in the development of medicines for the treatment of respiratory diseases based on bilirubin nanoparticles (BRNPs) (Chen *et al.*, 2020). Bilirubin nanoparticle drugs have been shown to attenuate T2-mediated lung inflammation and experimental asthma symptoms in mouse models (Kim *et al.*, 2017). It is believed that these medicines can be powerful ROS scavengers and an immunomodulatory agent for the treatment of lung diseases. In addition, these drugs demonstrate good safety in animal experiments, since the amount of bilirubin used in nanopreparations is small and does not create its toxic concentration. Indeed, recent studies in animal models have shown that the delivery of bilirubin to certain cellular targets using nanoparticles can have beneficial anti-inflammatory effects in chronic diseases (Chen *et al.*, 2020).

Keum *et al.* demonstrated that BRNPs have the potential to be used as a new therapy for the treatment of pulmonary fibrosis (Keum *et al.*, 2021). In a mouse model of pulmonary fibrosis, it was shown that BRNPS, localized in inflamed areas of lung tissue with progressive fibrosis, internalize in phagocytic inflammatory cells and alveolar epithelial cells, and by reducing the total level of ROS in the lungs, slow down the progression of the disease. As shown in this work, the removal of excess ROS using BRNP prevents the transmission of apoptotic signals and the release of chemokines penetrating into immune cells, as well as a significant decrease in the differentiation of epithelial cells and fibroblasts into myofibroblasts (Keum *et al.*, 2021). Bilirubin nanoparticle drugs are also suggested to have potential as a therapeutic option for preventing pulmonary fibrosis associated with Covid-19 infection.

In addition, there is evidence that medicines that induce hemoxygenase 1 or inhibit UDP-glucuronyltransferase A1 can increase the level of unconjugated bilirubin in blood serum to 1.0–3.5 mg/dl (Vitek *et al.*, 2023).

Strategies targeting modification of HO-1 activity, including genetic or chemical modulation of HO-1 expression, demonstrate therapeutic potential in inflammatory conditions (Ryter, 2022).

Conclusion

Currently, data are accumulating on the protective effect of bilirubin on a number of diseases due to its antioxidant properties. There is little information about the effect of upper-normal serum bilirubin concentrations in protecting the respiratory tract from environmental stressors and from the development of asthma in childhood. The relationship between bilirubin levels and asthma risk has been shown to follow a parabolic relationship, with moderately low and extremely high bilirubin levels causing a greater risk of developing asthma.

The ability of bilirubin to scavenge reactive oxygen species and inhibit the production of pro-inflammatory cytokines makes bilirubin a potential candidate for the development of therapeutic agents, including in aerosol form, intended to prevent bronchial asthma. Bilirubin may also have potential as a preventive agent against pathological airway remodeling in asthma. Currently, there is little information about the effect of different levels of bilirubin on respiratory function in children, which undoubtedly requires further research in this direction. In recent years, there has been interest in developing drugs for the treatment of respiratory diseases based on bilirubin nanoparticles. There is also a need for comprehensive pharmacological studies to test medicines capable of modulating bilirubin levels by inducing hemoxygenase 1 or inhibiting UDP-glucuronyltransferase A1.

References

AOKI J., INOUE A. & OKUDAIRA S. (2008): Two pathways for lysophosphatidic acid production. *Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids* **1781**(9), 513–518.

BARAÑANO D.E., RAO M., FERRIS C.D. & SNYDER S.H. (2002): Biliverdin reductase: a major physiologic cytoprotectant. *Proceedings of the national academy of sciences* **99**(25), 16093–16098.

BIANCO A., DVOŘÁK A., CAPKOVÁ N., GIRONDE C., TIRIBELLI C., FURGER C., VITEK L. & BELLAROSA C. (2020): The Extent of Intracellular Accumulation of Bilirubin Determines Its Anti- or Pro-Oxidant Effect. *Int J Mol Sci* **21**(21), 8101.

BORISKINA O.S., ELISEEVA T.I., TUSH E.V., KHRAMOVA R.N., SOODAEVA S.K., OVSYANNIKOV D.YU., E.V. PAVLOVA, ISHARINA A.N., KUBYSHEVA N.I., KHALETSKAYA O.V., NOVIKOV D.V. & NOVIKOV V.V. (2023): Relationship between the serum bilirubin level and the spirometric parameters in adolescents with bronchial asthma. *Pediatria n.a. G.N. Speransky* **102**(5), 13–17. doi: 10.24110/0031-403X-2023-102-5-13-17.

CHEN Z., VONG C.T., GAO C., CHEN S., WU X., WANG S. & WANG Y. (2020): Bilirubin nanomedicines for the treatment of reactive oxygen species (ROS)-mediated diseases. *Molecular pharmaceutics* **17**(7), 2260–2274.

CREEDEN J.F., GORDON D.M., STEC D.E. & HINDS JR T.D. (2021): Bilirubin as a metabolic hormone: The physiological relevance of low levels. *American Journal of Physiology-Endocrinology and Metabolism* **320**(2), E191-E207.

CURJURIC I., IMBODEN M., ADAM M., BETTSCHART R.W., GERBASE M.W., KÜNZLI N., ROCHAT L., ROTHE T.B., SCHWARTZ J., STOLZ D., TSCHOPP J-M., VON ECKARDSTEIN A., KRONENBERG F. & PROBST-HENSCH N.M. (2014): Serum bilirubin is associated with lung function in a Swiss general population sample. *European Respiratory Journal* **43**(5), 1278–1288.

FLACK K.D., VÍTEK L., FRY C.S., STEC D.E. & HINDS JR T.D. (2023): Cutting edge concepts: Does bilirubin enhance exercise performance? *Frontiers in Sports and Active Living* **4**, 1040687.

FREDENBURGH L.E., PERRELLA M.A. & MITSIALIS S.A. (2007): The role of heme oxygenase-1 in pulmonary disease. *Am J Respir Cell Mol Biol* **36**, 158–165.

GEORAS S.N., BERDYSHEV E., HUBBARD W., GORSHKOVA I.A., USATYUK P.V., SAATIAN B., MYERS A.C., WILLIAMS M.A., XIAO H.Q., LIU M. & NATARAJAN V. (2007): Lysophosphatidic acid is detectable in human bronchoalveolar lavage fluids at baseline and increased after segmental allergen challenge. *Clinical & Experimental Allergy* **37**(3), 311–322.

HAGA Y., TEMPERO M.A., KAY D. & ZETTERMAN R.K. (1996): Intracellular accumulation of unconjugated bilirubin inhibits phytohemagglutin-induced proliferation and interleukin-2 production of human lymphocytes. *Dig Dis Sci* **41**(7), 1468–74.

Hong F., Pan S., Guo Y., Xu P., Zhai Y. (2019): PPARs as nuclear receptors for nutrient and energy metabolism. *Molecules* **24**(14), 2545.

JAMEEL N.M., FREY B.M., FREY F.J., GOWDA T.V. & VISHWANATH B.S. (2005): Inhibition of secretory phospholipase A(2) enzyme by bilirubin: a new role as endogenous anti-inflammatory molecule. *Mol Cell Biochem* **276**, 219–25.

JANGI S., OTTERBEIN L. & ROBSON S. (2013): The molecular basis for the immunomodulatory activities of unconjugated bilirubin. *Int J Biochem Cell Biol* **45**(12), 2843–51.

JOSHI V., UMASHANKARA M., RAMAKRISHNAN C., NANJARAJ URS A.N., SUVILESH K.N., VELMURUGAN D., RANGAPPA K.S. & VISHWANATH B.S. (2016): Dimethyl ester of bilirubin exhibits anti-inflammatory activity through inhibition of secretory phospholipase A2, lipoxygenase and cyclooxygenase. *Archives of biochemistry and biophysics* **598**, 28–39.

JUNG J. & HWANG D. (2022): Genetic polymorphism of ADAM17 and decreased bilirubin levels are associated with allergic march in the Korean population. *BMC Med Genomics* **15**(1), 21.

KEUM H., KIM D., KIM J., KIM T.W., WHANG C.H., JUNG W. & JON S. (2021): A bilirubin-derived nanomedicine attenuates the pathological cascade of pulmonary fibrosis. *Biomaterials* **275**, 120986.

KIM D.E., LEE Y., KIM M., LEE S., JON S. & LEE S.H. (2017): Bilirubin nanoparticles ameliorate allergic lung inflammation in a mouse model of asthma. *Biomaterials* **140**, 37–44.

KIPP Z.A., XU M., BATES E.A., LEE W.H., KERN P.A. & HINDS JR T.D. (2023): Bilirubin levels are negatively correlated with adiposity in obese men and women, and its catabolized product, urobilin, is positively associated with insulin resistance. *Antioxidants* **12**(1), 170.

KUZNIEWICZ M.W., NIKI H., WALSH E.M., MCCULLOCH C.E. & NEWMAN T.B. (2018): Hyperbilirubinemia, phototherapy, and childhood asthma. *Pediatrics* **142**(4).

LEVI A.J. & ARIAS I.M. (1969): Two hepatic cytoplasmic protein fractions, Y and Z, and their possible role in the hepatic uptake of bilirubin, sulfobromophthalein, and other anions. *The Journal of clinical investigation* **48**(11), 2156–2167.

LEWIS B.W., FORD M.L., ROGERS L.K. & BRITT JR R.D. (2021): Oxidative stress promotes corticosteroid insensitivity in asthma and COPD. *Antioxidants* **10**(9), 1335.

LI Y., SHENG H., YAN Z., GUAN B., QIANG S., QIAN J. & WANG Y. (2022): Bilirubin stabilizes the mitochondrial membranes during NLRP3 inflammasome activation. *Biochemical Pharmacology* **203**, 115204.

Liu Y. (2008): Bilirubin possesses powerful immunomodulatory activity and suppresses experimental autoimmune encephalomyelitis. *Journal of Immunology* **181**(3), 1887–97.

LV J., SU W., YU Q., ZHANG M., DI C., LIN X., WU M. & XIA Z. (2018): Heme oxygenase-1 protects airway epithelium against apoptosis by targeting the proinflammatory NLRP3-RXR axis in asthma. *J Biol Chem* **293**(48), 18454–18465.

MEDIAVILLA M.G., PASCOLO L., RODRIGUEZ J.V., GUIBERT E.E., OSTROW J.D. & TIRIBELLI C. (1999): Uptake of [3H] bilirubin in freshly isolated rat hepatocytes: role of free bilirubin concentration. *FEBS letters* **463**(1-2), 143–145.

MICHAELOUDES C., ABUBAKAR-WAZIRI H., LAKHDAR R, RABY K., DIXEY P., ADCOCK I.M., MUMBY S., BHAVSAR P.K. & CHUNG K.F. (2022): Molecular mechanisms of oxidative stress in asthma. *Molecular aspects of medicine* **85**, 101026.

MURACA M. & FEVERY J. (1984): Influence of sex and sex steroids on bilirubin uridine diphosphate-glucuronosyltransferase activity of rat liver. *Gastroenterology* **87**(2), 308–13.

NADEEM A., SIDDIQUI N., ALHARBI N.O. & ALHARBI M.M. (2014): Airway and systemic oxidant-antioxidant dysregulation in asthma: a possible scenario of oxidants spill over from lung into blood. *Pulmonary pharmacology & therapeutics* **29**(1), 31–40.

PETERSEN C. & SUBBARAO P. (2021): Nudging the bilirubin dial to protect against asthma development. *J Allergy Clin Immunol* **148**(1), 78–79.

REDDEL H.K., BACHARIER L.B., BATEMAN E.D., BRIGHTLING C.E., BRUSSELLE G.G., BUHL R., BUHL R., CRUZ A.A., DUIJTS L., DRAZEN J.M., FITZGERALD J.M., FLEMING L.J., INOUE H., KO F.W., KRISHNAN J.A., LEVY M.L., LIN J., MORTIMER K., PITREZ P.M., SHEIKH A.,

YORGANCIOGLU A.A., & BOULET, L.P. (2022): Global Initiative for Asthma Strategy 2021: executive summary and rationale for key changes. *American journal of respiratory and critical care medicine* **205**(1), 17–35.

RYTER S.W., MORSE D. & CHOI A.M. (2007): Carbon monoxide and bilirubin: potential therapies for pulmonary/vascular injury and disease. *Am J Respir Cell Mol Biol* **36**, 175–182.

RYTER S.W. (2022): Heme oxygenase-1: an anti-inflammatory effector in cardiovascular, lung, and related metabolic disorders. *Antioxidants* **11**(3), 555.

SACKESEN C., ERCAN H., DIZDAR E., SOYER O., GUMUS P., TOSUN B.N., BÜYÜKTUNCER Z., KARABULUT E., BESLER T. & KALAYCI O. (2008): A comprehensive evaluation of the enzymatic and nonenzymatic antioxidant systems in childhood asthma. *J Allergy Clin Immunol* **122**(1), 78–85.

SCHERBININA M.B. (2007): Low blood bilirubin level: possible diagnostic and prognostic importance. *Clinical medicine* **85**(10), 10-14. (In Russ.).

SHAPIRA U., BREZINSKI R.Y., ROGOWSKI O., ZELTSER D., BERLINER S., SHAPIRA I., SHANITSARFATY S. & FIREMAN E. (2021): Association between elevated serum bilirubin levels with preserved lung function under conditions of exposure to air pollution. *BMC Pulmonary Medicine* **21**, 1–7.

SILVA S.L., VAZ A.R., BARATEIRO A., FALCÃO A.S., FERNANDES A., BRITO M.A., SILVA R.F.M. & BRITES D. (2010): Features of bilirubin-induced reactive microglia: from phagocytosis to inflammation. *Neurobiology of disease* **40**(3), 663–675.

STOCKER R., YAMAMOTO Y., MCDONAGH A., GLAZER A. & AMES B. (1987): Bilirubin is an antioxidant of possible physiological importance. *Science* **235**(4792), 1043–1046.

TAGER A.M., LACAMERA P., SHEA B.S., CAMPANELLA G.S., SELMAN M., ZHAO Z., POLOSUKHIN V., WAIN J., KARIMI-SHAH B.A., KIM N.D., HART W.K., PARDO A., BLACKWELL T.S., XU Y., CHUN J. & LUSTER A.D. (2008): The lysophosphatidic acid receptor LPA1 links pulmonary fibrosis to lung injury by mediating fibroblast recruitment and vascular leak. *Nature medicine* **14**(1), 45–54.

TAN N.S., SHAW N.S., VINCKENBOSCH N., LIU P., YASMIN R., DESVERGNE B., WAHLI W. & NOY N. (2002): Selective cooperation between fatty acid binding proteins and peroxisome proliferator-activated receptors in regulating transcription. *Mol Cell Biol* **22**(14), 5114–27.

THAM E.H., LOO E.X.L., GOH A., TEOH O.H., YAP F., TAN K.H., GODFREY K.M., VAN BEVER H., LEE B.W., CHONG Y.S. & SHEK L.P. (2019): Phototherapy for neonatal hyperbilirubinemia and childhood eczema, rhinitis and wheeze. *Pediatr Neonatol* **60**(1), 28–34.

TURI K.N., MCKENNAN C., GEBRETSADIK T., SNYDER B., SEROOGY C.M., LEMANSKE JR R.F., ZORATTI E., HAVSTAD S., OBER C., LYNCH S., MCCAULEY K., YU C., JACKSON D.J., GERN J.E. & HARTERT T.V. (2021): Unconjugated bilirubin is associated with protection from early-life wheeze and childhood asthma. *Journal of Allergy and Clinical Immunology* **148**(1), 128–138.

VITEK L. (2017): Bilirubin and atherosclerotic diseases. *Physiol. Res* **66**, S11–S20.

VITEK L., HINDS T.D., STEC D.E. & TIRIBELLI C. (2023): The physiology of bilirubin: Health and disease equilibrium. *Trends in Molecular Medicine*.

WAGNER K.H., WALLNER M., MÖLZER C., GAZZIN S., BULMER A.C., TIRIBELLI C. & VITEK L. (2015): Looking to the horizon: the role of bilirubin in the development and prevention of age-related chronic diseases. *Clinical science* **129**(1), 1–25.

WANG C., JIN C., YIN X., LIU J. & LIU J. (2021): Relationship between serum bilirubin concentration and sarcopenia in patients with type 2 diabetes: a cross-sectional study. *Journal of International Medical Research* **49**(3), 03000605211004226.

ZHAO M.M., KREBS J., CAO X., CUI J., CHEN D.N., LI Y., HUA L., MANN J. & YANG J.K. (2019): Helicobacter pylori infection as a risk factor for serum bilirubin change and less favourable lipid profiles: a hospital-based health examination survey. *BMC infectious diseases* **19**, 1–8.