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USE OF CURCUMIN AND ITS DERIVATES IN PREVENTION AND TREATMENT OF HYPEROXIA-DERIVED RESPIRATORY DISEASES IN PRETERM INFANTS: A SUMMARY REVIEW

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Abstract: Oxygen therapy is necessary in preterm infants, but inhalation of high concentrations of oxygen (hyperoxia) has a toxic effect on pulmonary function. Respiratory injuries in these children arise due to: their depressed antioxidant enzyme status, toxicity of oxygen, volume and barotrauma during mechanical ventilation. The researches has shown that curcumin has antioxidant properties (removes various forms of free radicals) and anti-inflammatory properties (suppresses inflammation through different mechanisms). But its relatively low bioavailability and chemical instability restrict its application. Researches has shown that its derivates have improved bioavailability and pharmacological activities. The aim of this review article is to summarize the effects of curcumin and its derivates in controlling the inflammation and oxidative stress of the lungs in preterm infants exposed to oxygen therapy.

Keywords: (2E, 6E)-2,6-bis[(2-trifluoromethyl)benzylidene]-cyclohexanone; (2E, 6E)-2,6-bis(2-bromobenzylidene)cyclohexanone; oxygen; inflammation; lungs; rats; bioavailability; application; therapy.

INTRODUCTION

Premature birth is a very serious health problem and a leading cause of infant mortality worldwide (WHO, 2012). Each year about 15 million babies (more than one in ten children) are born prematurely, and more than one million babies die shortly after birth (Liu et al., 2016). Premature birth, ie, prematurity is the birth of a baby before the 37th week of gestation, whereas before the 28th week of gestation is considered extreme prematurity. The rate of premature births in developed countries is about 7% and it is constantly growing (Cosgrave, Scott, Goble, 2008). This increase is associated with the increased number of multiple pregnancies and births,

and the alterations of the characteristics of the mother (the majority of mothers today are older than 35 years, and also there are too young mothers or with high-risk pregnancies) that occur frequently nowadays.

Premature birth causes the infant to be born before the lungs are fully formed and able to carry out adequate gas exchange. Hypoxia and anoxia that occur due to incomplete maturation of the lungs in premature infants is a condition that the small organism is not able to correct, therefore prompt and professional intensive care since birth is required with monitoring and timely response to any change in the situation which can occur in preterm babies (Guyton & Hall, 2003).

The application of oxygen therapy (oxygen therapy) is used quite often in neonatology, especially in premature babies (Smith et al., 2010). Giving oxygen therapy depends on gestational week of birth, and a particular indication for its use is extreme prematurity. Although this therapy significantly reduced the rate of infant mortality, recent studies have shown that even short exposure to oxygen causes long-lasting changes in biochemical markers of oxidative stress (Vento, Moro, Escrig et al., 2009) and has adverse consequences on pulmonary function. Hence, the use of oxygen therapy carries a risk, like any other drug.

The increased occurrence of respiratory diseases, especially in extremely premature infants (23-26 weeks) is primarily due to the immaturity of their lungs and oxygen toxicity. Inhalation of high concentrations of oxygen (hyperoxia) has a toxic effect on pulmonary function and according to the researches it leads to release of reactive oxygen species (Barazzone & White, 2000). The toxicity of oxygen creating cytotoxic free oxygen radicals and insufficient antioxidant defense mechanisms of newborns, lead to lung damage and may also increase the risk of airway hyperresponsiveness, asthma, reduced lung function and altered responses to respiratory viral infections later in childhood. The appearance of airway hyperresponsiveness in hyperoxia is due to increased contraction of smooth muscle cells, thickening of muscles and elastin production.

Hyperoxia, also, stimulates the formation of inflammatory processes in the lung tissues. Inflammation caused by hyperoxia appears particularly acute in the early stages of the acute injury. Hyperoxia also stimulates the release of a number of proinflammatory cytokines such as: tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) (Ogawa, Tasaka, Yamada et al., 2007). In infants with very low birth weight, even short-term inhalation of high concentration of oxygen after birth leads to release of cytokines and inflammatory cascade that is an introduction in the incidence of bronchopulmonary dysplasia, which is proved by experimental and clinical studies (Jensen & Schmidt, 2014).

Supplementary oxygen is inevitable for the treatment of the premature infants, and therefore lot of research has been done for resolving the problem with the lung damage that arise from exposure to it. Recently, the attention of scientists and researchers is focused on the herbal products. One of these compounds is curcumin and its derivates, because of their numerous biological properties.

MEDICAL RESEARCHES FOR UNDERSTANDING THE HYPEROXIA-DERIVED RESPIRATORY DISEASES IN PRETERM INFANTS

The application of oxygen in preterm infants is necessary to prevent hypoxemia and allow normal growth and development of cells of all organs. But, administration of high concentrations of oxygen causes side effects.

Medical advances in the understanding of the hyperoxia-derived respiratory diseases in preterm infants and the potential for development of therapeutic strategies have been achieved by using large (baboons, sheep and pigs) and small (rabbits, rats and mice) animal models. Researchers Warner et al. (1998) found that there are more advantages if small animal models are used for the study of respiratory diseases caused by the high concentration of oxygen, such

as lower costs, easier maintenance, ability to work with a larger number of animals on a study and larger capacity for genetic manipulation in these animals.

In 1976, Northway and colleagues proved that newborn mice exposed to 100% oxygen develop phenotype that is similar to bronchopulmonary dysplasia. Recent studies have shown that mice exposed to 100% oxygen at the time of birth, develop changes and diseases of the lungs, leading to shortening of their life (Yee et. al., 2011).

Studies with rats showed that neonatal rats are virtually resistant to the lethal effects of hyperoxia, while sexually mature rats under the influence of hyperoxia have 100% mortality (Frank, Bucher, Roberts, 1978). This difference is due to the activity of antioxidative enzymes in the lungs of newborn rats whose response was not observed in mature rats (Hoffman & Stevens, 1980). However, despite the resistance of mortality, it was revealed that exposure of neonatal rats to severe hyperoxia (> 97%) leads to a reduction of the total lung volume and expiratory volume (Randell, Mercer, Young, 1990). Studies have also shown that exposure of neonatal rats to hyperoxic gas has harmful effects, particularly to the structure of the region for gas exchange (O'Reilly, Thébaud, 2014). Oxygen toxicity in neonatal rats causes parenchymal and vascular lung damage that continue into adulthood (Wilson et al., 1985).

Hence, we can sum up that the use of neonatal mice and rats as preclinical models for testing different therapeutic strategies and development of appropriate therapeutic agents for hyperoxia-derived respiratory diseases has been proved to be quite effective.

RESEARCHES RELATED TO THE ROLE OF CURCUMIN IN PREVENTION AND TREATMENT OF RESPIRATORY DISEASES

Curcumin is bright yellow pigment found in the rhizomes of turmeric (*Curcuma Longa*), which is a member of the family of ginger (*Zingiberaceae*) with a wide range of pharmacological activity (Aggarwal, Kumar, Bharti, 2003; Ammon, 1991). Curcumin is the primary polyphenol obtained from turmeric through the process of extraction. Antioxidant and anti-inflammatory mechanisms are the two main mechanisms which are responsible for most of the effects of curcumin in different conditions (Lin et. al., 2007; Marchiani et al. 2014).

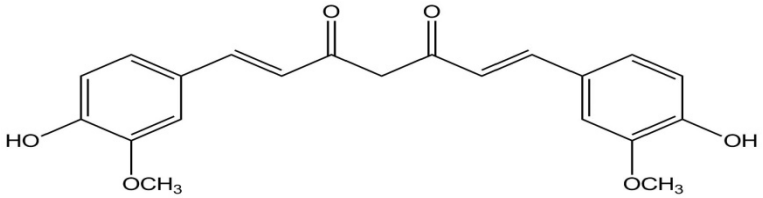


Figure 1. Chemical structure of curcumin

Curcumin has been shown that enhances systemic markers of oxidative stress (Sahebkar et al., 2015). There are several different mechanisms by which curcumin's effects are carried out on free radicals. Curcumin removes various forms of free radicals such as reactive oxygen and nitrogen species (Menon, Sudheer, 2007), it can alter the activity of enzymes responsible in the neutralization of free radicals, such as glutathione, catalase and superoxide dismutase (Lin et. al., 2007; Marchiani et al. 2014) and may inhibit enzymes that accelerate the release of free radicals, such as lipoxygenase/cyclooxygenase and xanthine dehydrogenase/oxidase (Lin et. al., 2007).

Many inflammatory cells release a number of reactive species at the site of inflammation, suggesting that there is a link between oxidative stress and inflammation (Biswas, 2016). Tumor necrosis factor (TNF-α) is one of the main mediators of inflammation in many diseases, and its effect is regulated by the activation of the transcription factor, nuclear factor NF-κB. TNF-α is the strongest activator of NF-κB, and its expression is regulated by NF-

κB. It is proven, curcumin blocks the activation of NF-κB, which is increased by the activity of several different inflammatory stimuli (Panahi et al., 2016).

One study suggests that curcumin effectively reduces airway inflammation in asthmatic mice and decreases the expression of proinflammatory cytokines, possibly through Nrf2/HO-1 signaling path (Liu et al., 2015). Therefore, it is thought to be a potential drug for the treatment of asthma. According to another study (Subhashini et al., 2016), conducted in 6-8 weeks old mice, it has been showed that curcumin is anti-inflammatory molecule with strong anti-asthmatic potential and it suppresses asthma characteristics: inhibition of inflammation of the airways and bronchoconstriction if applied through nasal route.

The results of another study indicated that *Curcuma longa* and its components have preventive effects on total and differential WBC (white blood cells in the blood), serum levels of NO_2, NO_3, MDA, CAT and thiol group in animal models of asthma (male adult Wistar rats) which is comparable to the effects of dexamethasone already used concentrations (Shakeri, Soukhtanloo, Boskabady, 2017).

Clinical and preclinical studies suggest that curcumin is extremely well tolerated. Even at high doses it has been shown that curcumin is not toxic to humans and animals. But although tolerability of curcumin is extremely good, it has been shown that curcumin has poor *in vivo* bioavailability, which is particularly important feature of this natural polyphenol used in numerous medical purposes. Clinical studies in which healthy subjects took 2 g of pure curcumin powder showed that curcumin levels in serum is almost impossible to detect (Shoba et al., 1998). Hence, the use of curcumin as a therapeutic agent in hyperoxia-derived respiratory diseases in preterm babies is limited.

APPLICATION OF CURCUMIN DERIVATIVES IN THE MANAGEMENT OF HYPEROXIA-DERIVED RESPIRATORY DISEASES IN PRETERM INFANTS

Most of the researches on curcumin derivates were conducted for cardiovascular applications. The researchers studied the beneficial effects in prevention or treatment of cardiovascular diseases of the natural and synthetic derivatives of curcumin.

For example, it was found that compound (2E, 6E)-2,6-bis[(2-trifluoromethyl) benzylidene]cyclohexanone - C66 has a favorable effects in pharmacological complications that occur in diabetes disease due to its anti-inflammatory effect (Pan et al., 2012). C66 was also found that has a protective effect against pathogenic changes of the aorta caused by diabetes in experimental animal models of 6-8 weeks old male mice. C66 treatment prevented the progression of diabetes-induced aortic inflammation, oxidative damage, apoptosis and fibrosis (Li et al., 2018). Also, researchers found that C66 has a favorable effect on diabetic nephropathy through the mitogen-activated protein kinase (MAPK)-dependent anti-inflammatory or anti-ACE (angiotensin converting enzyme) mechanism (Pan, Huang, Wang et al., 2014). But, this compound had poor antioxidant activity (Ren & Sowers, 2014).

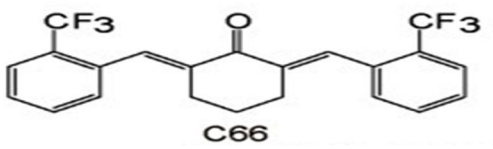
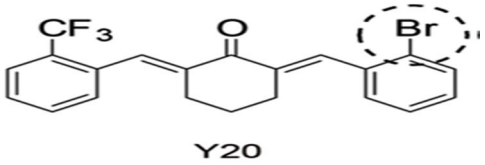


Figure 2. Chemical structure of curcumin derivate C66

In additional studies it was confirmed that other ingredient (2E, 6E)-2-(2-bromobenzyliden)-6-[(2-trifluoromethyl) benzylidene]cyclohexanone (so called Y-20) has better antioxidant properties than C66 and it is safe to use with no side effects (Küpper et. al., 2013). Küpper and his associates, found that the beneficial properties of Y20 are associated

with the ability of this compound to increase the expression of Nrf2 and inhibit activation of NF-κB. The results of studies have shown that these compounds have potential in the treatment of heart diseases caused by obesity, using Nrf2 and NF-κB as targets for the treatment of diseases associated with obesity.



Y20

Figure 3. Chemical structure of curcumin derivate Y20

However, there are no studies related to the effects of curcumin derivates on respiratory diseases.

CONCLUSION

Anti-inflammatory and antioxidative properties of curcumin and curcumin derivates are described in a number of studies in the literature, but they are not often associated with respiratory diseases. Furthere more, there are no studies related to the effects of newly synthesized curcumin derivates on hyperoxia-derived respiratory diseases in preterm infants. We conclude that further research on the effects of curcumin derivatives in critical acute phase of hyperoxic damage to the airways should be conducted, and whether they can be used as therapeutic agents during oxygen therapy, which would significantly reduce the rate of respiratory diseases, which occur in premature infants receiving suplemental oxygen.

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