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Antitumor effect of curcumin and carnosic acid (literature review)

Relevance: *Natural polyphenols play an important role in the treatment of many diseases, including cancers. Polyphenols obtained from food such as curcumin and carnosic acid, attract increased research interest due to their beneficial effects on human health. As antioxidants, they have anti-proliferative and anti-inflammatory effects in various diseases.*

The purpose of this study *was to review and analyze published data on the effects of curcumin and carnosic acid on the human body.*

Results: *The published research results indicate the possibility of using curcumin and carnosic acid for medicinal purposes.*

Curcumin has antioxidant, anti-inflammatory and anti-amyloid, antidepressant, immunomodulatory effects, anti-carcinogenic properties. It affects metabolism, membrane potential, oxidative stress, respiration, and cell cycle and can induce apoptosis in cancer cells without cytotoxic impact on healthy cells.

Carnosic acid is highly active in neutralizing free radicals, has an antioxidant, pronounced antibacterial, antifungal, anti-inflammatory activity, participates in cell regeneration and restoration of cell division and renewal to prevent aging, stabilizes the production of enzymes by normalizing the digestion, and affects brain activity by improving mental abilities. Thanks to the anti-static and anti-tumor effects, it suppresses the proliferation of fast-growing cells.

Conclusion: *The preparations containing curcumin and carnosic acid were found to have significant therapeutic potential in treating many diseases, including cancers.*

Keywords: *natural polyphenols, curcumin, carnosic acid, malignant tumors, antioxidants, antitumor effect.*

Introduction: Polyphenols attract attention of nutritionists and scientists working on raising the value of food products. They study the healing effects of polyphenols and their possible use for treating pancreatic cancer [1]. In everyday life, the effectiveness of polyphenols directly depends on their quantity and bioavailability in dietary products. Their action (polymerization, esterification, acetylation, methylation and esterification) depends on their chemical structure, food matrix and metabolism. The effectiveness of the absorption of polyphenols in the digestive tract varies and affects their impact on the signaling pathways they modulate. Polyphenols modulate key proteins in signaling cascades associated with the differentiation of cells in the body during proliferation and metastasis, or apoptosis [2].

The history of studying properties of polyphenols is a good example of shifting the emphases in the consistent discovery of new chemical properties and biological effects, as well as a gradual change of paradigms in studying human physiology and the views on disease and health. According to the "biochemical" concept which prevailed in the beginning, the antioxidant properties of polyphenols explained their biological effects and, primarily, their ability to prevent chronic diseases, namely, the pathologies associated with oxidative stress, such as cancer, obesity and neurodegenerative, cardiovascular diseases, type II diabetes and inflammation [3]. The search for the possible uses of the effects of plant-derived polyphenolic compounds is actualized every year due to the continued discovery of their abilities to act on different levels (from cellular and molecular to whole-body), which expand their possible application in medicine.

The purpose of this study was to review and analyze published data on the effects of curcumin and carnosic acid on the human body.

Materials and methods: The paper represents the analysis of published studies of medicinal properties of plant-derived polyphenols, in particular, curcumin and carnosic acid. The sources included fundamental studies, articles in periodical scientific journals, scientific conference abstracts. The search was conducted using the following keywords: «polyphenols of natural origin,» «curcumin,» «carnosic acid,» «malignant tumors,» «antioxidants,» «antitumor effect.»

Results and discussions:

Polyphenols are natural food compounds found mainly in fruits and vegetables. To date, more than 8,000 polyphenolic compounds have been identified in the human menu [4]. Polyphenolic compounds are secondary metabolites of plants which contain one or more hydroxyl (—OH) groups attached to the —ortho, —meta on the benzene ring. These metabolites usually participate in protecting the plant from ultraviolet radiation, the impact of various environmental pollutants and pathogens [5]. Polyphenols are polyhydroxy phytochemicals that have similar structural components, like conjugated closed rings and hydroxyl groups [6]. The most common polyphenols are classified by their chemical structure and orientation of bonded phenolic rings into four main subclasses: flavonoids (60%), phenolic acids (30%), stilbenes, and curcuminoids [7]. The medicinal properties of curcuma (Figure 1) were known for thousands of years; however; its bioactive components and precise mechanisms of action were discovered only in recent decades [8]. Curcuma is a natural

antibiotic and immunomodulator [9]. Curcumin and its derivatives have anti-inflammatory, antioxidant and anti-carcinogenic properties [10].

Curcumin is the principal curcuminoid contained in the Curcuma root. Other curcuminoids are dimethoxy curcumin and bis-dimethoxy curcumin. Curcuminoids are responsible for the characteristic orange-yellow color of the Curcuma root. Curcumin is insoluble in water, poorly soluble in diethyl ether, and readily soluble in alcohol. Curcumin does not change its color in mineral acid solutions but dissolves and turns red-brown in alkalis. In the ethanol solution, it is absorbed at wavelength of λ_{max} = 430nm [11].

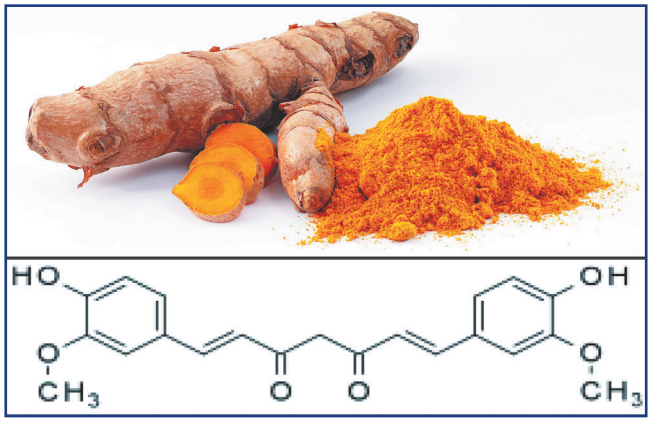

Figure 1 – Curcumin powder from curcuma root and its chemical structure [12]

Curcumin is intensively studied as a potential medicine, in particular, as an antitumor drug. Curcumin can cause apoptosis of cancer cells while not being toxic for healthy cells [13]. Curcumin has an antioxidant, anti-inflammatory, and anti-amyloid action. The antidepressant effect of curcumin is realized through the inhibition of monoamine oxidase [14]. Curcumin is active on the cellular level and mainly targets multiple signaling molecules [15].

One of the main problems of using curcumin is its low bioavailability [16] which is mainly due to its poor absorption, rapid metabolism, and rapid elimination. Most studies, therefore, focus on developing the drugs that block metabolic pathways of curcumin in order to increase its bioavailability. For example, piperine (the main active ingredient is black pepper) [17] increases the bioavailability of curcumin by 100% [18]. Thus, the problem of poor bioavailability can be solved by adding such agents.

Anti-inflammatory effects and antioxidant properties of curcumin. the formation of free radicals in the cells and intercellular space is one of the most universal processes in the vital activity of any organism. The release of several reactive radicals by inflammatory cells at the site of inflammation leads to oxidative stress. It demonstrates the relationship between oxidative stress and inflammation [19]. Oxidative stress (the process of cell damage due to oxidation) is involved in many chronic diseases, and its pathological processes are closely associated with inflammatory diseases. At the same time, several reactive oxygen/nitrogen types can initiate an intracellular signaling cascade that enhances pro-inflammatory gene expression. In most diseases, the inflammation is mainly mediated by tumor necrosis factor α (TNF-α) which is regulated by epy activation of the transcription factor, the nuclear factor (NF) -kB. TNF-α is considered the most potent activator of NF-kB, while NF-kB, in turn, regulates the TNF-α expression. TNF-α NF-κB is activated by most inflammatory cytokines, gram-negative bacteria, various pathogenic viruses, environmental pollutants, high glucose levels, ultraviolet radiation, and other disease-causing factors [20]. Agents that regulate NF-κB and gene products regulated by NF-κB have potential efficacy against the negative impact of such factors. Curcumin blocks the activation of NF-kB. Many different mechanisms curcumin can use to inhibit inflammation [21] make it a potential anti-inflammatory agent.

The antioxidant and anti-inflammatory properties of polyphenols are based on two main mechanisms that explain most of the effects of curcumin on various cellular mechanisms [22-23]. Curcumin is known to act on systemic markers of oxidative stress [24] increasing serum activity of antioxidants such as superoxide dismutase (SOD). Curcumin has a positive effect on prostate tumor [25]. Systemic review and metanalysis of randomized data on the efficacy of purified curcuminoid additives shows a significant effect of curcuminoids on all studied parameters of oxidative stress, including plasma activity of SOD and catalase, as well as concentration of glutathione peroxidase (GSH) and serum lipid peroxides. Different mechanisms are responsible for the impact of curcumin on free radicals. It can bind various forms of free radicals, such as reactive oxygen (ROS) and nitrogen (RNS) [26], or modulate the activity of GSH, catalase, and SOD enzymes active in neutralizing free radicals. Curcumin can also inhibit ROS-generating enzymes such as lipoxygenase/cyclooxygenase and xanthine hydrogenase/oxidase [27]. In addition, curcumin, being a lipophilic compound, effectively absorbs peroxyl radicals and therefore is also considered as an antioxidant that destroys the food chain [23].

Curcumin has been shown to weaken certain aspects of metabolic syndrome by improving insulin sensitivity [28-29], inhibiting adipogenesis [30], and lowering high blood pressure [31], inflammation [32] and oxidative stress [33-34]. In addition, there is evidence that curcuminoids modulate gene expression and activity of enzymes involved in lipoprotein metabolism thus decreasing plasma triglycerides and cholesterol [35–36] and increasing the HDL-C concentration [37]. The addition of curcumin to food was shown to significantly reduce the concentration of proinflammatory cytokines in serum in patients with MetC [38].

Carnosic acid is a plant-derived polyphenolic compound that attracts the attention of clinicians. Carnosic (or carnazolic) acid is not synthesized in the body, it is only ingested with food. Carnosic acid is found in large quantities in Rosemary and Salvia. The properties of carnosic acid allow its inclusion in some treatment and preventive drugs. Rosemary leaves are used as a seasoning and a food preservative. This aromatic herb does not only have a unique taste and smell but is an excellent raw material for a useful medicinal compound – carnosic acid (Figure 2) [39]. Rosemary leaves are included in the British Herbal Pharmaco-

poeia. In the US, India, and China, they make an official pharmacological raw material and are used in herbal medicine and homeopathy [40–41].

Figure 2 – Chemical structure of carnosic acid obtained from rosemary [49]

Rosemary polyphenols (in particular, carnosic acid) are one of the most powerful natural antioxidants used in food preservation, herbal medicine, as an anti-inflammatory and detoxifying agent. Active components of carnosic acid can stabilize the production of enzymes and normalize the digestive process. Certain metabolites of carnosic acid can affect brain activity and improve mental abilities [42]. The studies of carnosic acid on cell lines and animals have shown its anti-inflammatory, antioxidant, and antitumor activity. The primary property of carnosic acid is its high ability to neutralize free radicals, even in the human brain, thus preventing the disorders associated with poor neurotransmission which is registered in mental illness, increased sensitivity to stress and cognitive impairment. Carnosic acid could prevent or treat the conditions associated with reduced transmitter/mediator activity of dopamine, serotonin, and noradrenaline. Free radicals can cause inflammation, cancer development, and simply aging. Carnosic acid is valued for its effectiveness against aging and withering of brain cells which it can prevent [43–45]. Carnosic acid prevents aging by promoting cell regeneration and restoration of division and renewal processes [42]. Carnosic acid inhibits the nitric oxide synthase-induced down-regulation factor in mouse macrophages [46], cyclooxygenase (COX) -2- transcription in human breast epithelial cells [47]. Carnosic acid also induces Nrf-2 which an important transcriptional regulator of antioxidant, anti-inflammatory, and detoxification processes [48]. Rosemary essential oil exhibits pronounced antibacterial, antifungal, anti-inflammatory, cytostatic, antioxidant properties. Diterpene phenols of Rosemary and Salvia are efficient even in low concentrations and could perfectly replace synthetic antioxidants. Carnosic acid is capable of releasing free radicals in the cell structure and bind them for future transformation [49].

Carnosic acid is considered a substance with a very high antioxidant potential; it can inactivate peroxynitrite (a free nitrogen radical secreted by activated macrophages during inflammation), has a pronounced anti-inflammatory effect; it is an efficient antimicrobial agent; it can act against tumors due to a pronounced suppression of proliferation of rapidly growing cells [44].

All this substantiates a growing interest in the development of compounds that could be used in the food and pharmaceutical compositions for the treatment of disorders associated with impaired neurotransmission and for improving the learning ability and memory of those who are stressed or prone to psychiatric instability. The study of the mineral composition of Curcuma and Rosmarinus officinali is also relevant for the further use of these raw materials as a source of biologically active substances in the treatment of cancers.

Conclusion: The data published in the sources meeting the requirements of evidence-based medicine confirm a beneficial effect of Curcuma and Rosemary in pathological disorders in the division processes, in particular, oncological processes. This is due to the high content of polyphenols, such as curcumin and carnosic acid. Studies of the cellular mechanism of action of these polyphenolic compounds are focused on application in oncology and represent a promising strategy for increasing the efficiency of therapy of prostate cancer and cancers of other localizations.

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