Opinion

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Concept Notes on Carotenoid Metabolites

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Introduction

Carotenoids are tetraterpenoid consists of series of conjugated double bonds and they are liable to enzymatic or non-enzymatic oxidative breakdown or isomerization at various physiological conditions. Further, oxidation or isomerization can also occur during food processing and other chemical reactions. In general, biotransformation of carotenoids occurs through hydroxylation, epoxidation, isomerization and oxidation-reduction *in vivo*. Central cleavage of carotenoids gives C_{20} compounds retinoids, eccentric cleavages gives smaller fragments, notably C_{10}, C_{13} and C_{15} compounds with end group. Carotenoids are associated with reduced incidence of major health related problems such as vitamin-A deficiency, age-related macular degeneration, atherosclerosis, cancers and other chronic diseases [1]. Several epidemiological and clinical studies have addressed the precise role of carotenoids function in animal models and humans from past four decades. The role of carotenoids came into existence from identification of active metabolites of provitamin A carotenoids as retinal, retinol and retinoic acid. Enzymatic (central or eccentric) cleavages of β-carotene, α-carotene, and β-cryptoxanthin leads to the formation of retinoids [2]. These evidences demonstrate that carotenoids oxidative products/ molecules are involved in major biological functions. Recently, omics has attracted much attention of researchers due to active role of carotenoids metabolites at cellular levels [3]. Similarly, many studies including our own, support the concept that biological function are mediated by certain carotenoid metabolites [4-8]. Generally, oxidation products of carotenoids might be formed by reacting with reactive oxygen species [4,9]. A polar oxidation product of β-carotene, 5, 8-endoperoxy-2, 3-didhy-dro-β-apocarotene-13-one was shown to inhibit cell growth and cholesterol synthesis in MCF-7 mammary cancer cells [10]. However, in case of β-carotene and lycopene or its cleavage products may act as pro-oxidants under circumstances like higher O_2 tension in smokers when supplemented with high doses [11]. Likewise, retinoids potentiates the hepatotoxicity with consumption of alcohol in various animal models and humans [12]. Hence, occurrence, formation and characterization of oxidative/isomerised/enzymatic cleavage products of carotenoids are crucial to evaluate precise role against various biological functions. Furthermore, biochemical characterization of BCO2 demonstrates that, the enzyme also catalyses a non-provitamin A carotenoids like lycopene and lutein other than the provitamin A carotenoids [13]. Several key metabolites of lycopene, such as 2,6-cyclolycopene-1,5-diol, Apo-6'-,8'-,10-',12'-,and14'-lycopenal were identified in human tissue and milk [4,14]. A cleavage product of lycopene (E, E, E)-4-methyl-8-oxo-2, 4, 6-nonatrienal was shown to involve in apoptosis-inducing activity in HL-60 cells [15]. Consequently, lycopene degraded products also modulates the cell signalling through enhancing cell-to cell communication [16]. It is hypothesized that, formation of metabolites in biological actions may possibly involve in reduction of chronic diseases such as cancer. However the mode of action/mechanism of these metabolites is yet to be addressed.

In xanthophyll's, the functional groups (hydroxy-, epoxy- and keto-groups) may react rapidly with peroxyl radicals and forms number of oxidative products. Woodall et al. [17] suggested that position of substitution of radicals is an important factor that influences the rate of bleaching. The oxidized forms of carotenoids may be highly reactive, since oxidation results in radical ions, which can combine with similar reactive oxidative species that could lead to higher antioxidant effect [8]. Similarly, carotenoids with oxo- and hydroxyl functional groups may profoundly have antiradical actions [18]. In case of lutein metabolism, 3'-epilutein, 3'-dehydrolutein, (3R, 3'S)-*meso*-zeaxanthin, 3'-oxolutein, 3-methoxy-zeaxanthin and other isomers/metabolites have originated inherently due

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to oxidation [4,19]. Oxidative metabolites of these carotenoids could be involved in signal transduction, photo sensitization and act as antioxidant to protect the eyes from phototoxicity [19,20].

In case of keto-carotenoids, such as astaxanthin and canthaxanthin, found in certain algae, microorganisms and marine animals are considered as potent antioxidants [21]. Metabolites of astaxantin like, 3-hydroxy-4-oxo-β-ionol, 3-hydroxy-4-oxo-β-ionone, 3-hydroxy-4-oxo-7, 8-dihydro-β-ionol and 3-hydroxy-4-oxo-7, 8-dihydro-β-ionone were shown to be involved in xenometabolism in humans [22]. It was also hypothesized that, astaxanthin may also yield retinoid like molecules in marine fish and rats [23]. However, responsible enzymes for the formation of astaxanthin metabolites and their biological functions is not been elucidated. 3-Hydroxy-4-oxo-7, 8-dihydro-β-ionone a major urinary metabolite was detected in rats after administration of radiolabeled canthaxanthin [24]. Furthermore, 4-oxo-retinoic acid, an oxidation product of canthaxanthin activated RAR β-gene and enhanced cell communications [25].

Fucoxanthin found in brown seaweeds is attributed as a promising molecule against obesity and cancer. During intestinal absorption fucoxanthin is biotransformed into fucoxanthinol and amarouciaxanthin-A occurred in rodents [26]. In case of sea squirt, fucoxanthinol was further metabolized into halocynthiaxanthin [27]. More recently, it is reported that actions of fucoxanthinol in modulation of NF-κB pathway was more pronounced than fucoxanthin in MCF-7 and MDA-MB-231 cells [28].

The diversity of carotenoid metabolites have been studied from major carotenoids demonstrates, the necessity of possible modifications through various interactions mediated either by chemically or physically or enzymatically to serve the key biological functions. There are >750 carotenoids documented from various natural sources, investigation of these carotenoids and their products needs to be explored to understand bioactivity. This gives a platform and wide scope for the Nutritional biochemistry to obtain better molecules than existing or known carotenoids or its active metabolites. Further, role of notable metabolites towards modulation of cell communication, cellular signalling and molecular targeting needs to be detailed to explore beneficial and detrimental effects in cancer and other chronic diseases. Apart from elucidation of molecular function of carotenoids or metabolites, the isolation and characterization of such molecules is challenging in biological entity. Thus advancement in analytical techniques and optimization is more essential for the identification of molecules that are present in nanomolar/picomolar range in human serum and tissues.

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