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Review article

β-Ionone and its analogs as promising anticancer agents

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ABSTRACT

β-Ionone is an end-ring analog of β-carotenoids which widely distributed in fruit and vegetables. Recent studies have demonstrated anti-proliferative, anti-metastatic and apoptosis induction properties of β-ionone in vitro and in vivo. Also, the studies have focused on investigating the β-ionone action on different types of malignant cells and the possible mechanisms of action. Moreover, the quest of new synthetic β-ionone-based compounds possessing anti-proliferative, anti-metastatic and apoptosis induction activities may enable the discovery of compounds which can be used in combination regimes thus overcoming tumor resistance to conventional anticancer agents. These new agents will also be useful for targeting distinct signaling pathways, to activate selectively mechanisms for apoptosis in cancer cells but devoid of undesirable side effects. In this paper, we reviewed the potentialities of β-ionone and related compounds in cancer prevention and chemotherapy.

Contents

1. Introduction

β-Ionone (4-[2,6,6-trimethyl-1-cyclohexen-1-yl]-3-buten-2-

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one, Fig. 1), is a cyclic terpenoid compound that forms the basic nucleus structure of retinoic acid, retinol, β-carotene and vitamin A [1,2]. This compound which also known as a rose ketone substance was isolated from plant oils, such as oils from *Viola odorata*, *Boronia megastigma Nees*, *Petunia hybrida*, *Cistus monspeliensis*, *Lepidium meyenii*, *Medicago marina*, *Osmanthus fragrans*, *Rosa bourboniana*, *Thymus serpyllum* and additionally in different algae species. β-Ionone and other ionone derivatives also occur in fruits, vegetables and grains containing β-carotene, and thus they can be found in a various foods such as carrots, raspberries, roasted almond, tea, tangelo and tomato [3]. It also naturally occurs as a biogenic volatile organic compound and shows a ubiquitous incident in the air as a result of emissions from plants or surface waters. Additionally due to biotransformation processes in phytoplankton, β-ionone was found in concentrations ranging from 0.002 μg/L up to 1.2 μg/L in waters of lakes and rivers [4]. β-Ionone is a component that use in many fragrances. It was found in fragrances used in decorative cosmetics, fine fragrances, shampoos, toilet soaps and other toiletries [5].

Previous studies have demonstrated that β-ionone and its derivatives can exhibit significant pharmacological activities such as antileishmanial [6], anti-inflammatory [7], antifungal and antibacterial activities [8,9]. In particular, recent studies have demonstrated anti-proliferative, anti-metastatic and apoptosis induction properties of β-ionone in vitro and in vivo [10–13].

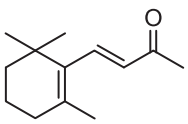
Considering cancer is the prominent cause of death worldwide and actually it becomes a severe threaten to human life and health, much more progressive attempts have been made to find out new potential and effective compounds to fight against this disease [14]. Also, many efforts have been focused on the discovery of compounds which can be used in combination regimes, thus overcoming tumor resistance to conventional anticancer agents [15].

This review critically describes the potential role of natural product β-ionone and related synthetic compounds in the chemoprevention and treatment of various cancers. Both in vitro and in vivo effects of β-ionone and its analogs and related cellular and molecular mechanisms are highlighted. Also, possible challenges and future directions involved in the development of promising β-ionone derived compounds in the chemoprevention and therapy of human cancers are discussed.

2. β-Ionone biochemistry

β-Ionone is a precursor for carotenoids, one of the most important group of natural pigments. As depicted in Fig. 2, the cleavage of α-carotene (**2**) by the recombinant enzymes leads to the production of α-ionone (**4**) and β-ionone (**1**). This process is mediated by the carotenoid dioxygenase enzyme [16]. Furthermore, β-ionone is a metabolite of β-carotene (**6**, Fig. 2). The oxidative cleavage of β-carotene finally resulted in the formation of β-ionone [17]. Also, β-ionone was prepared from the enzymatic oxidation of β-carotene by xanthine oxidase in aqueous solution through formation of free radical and utilizing of aldehyde as substrate [18].

Results from animal studies for β-ionone showed that it was



β-Ionone (**1**)

Fig. 1. Structure of β-ionone.

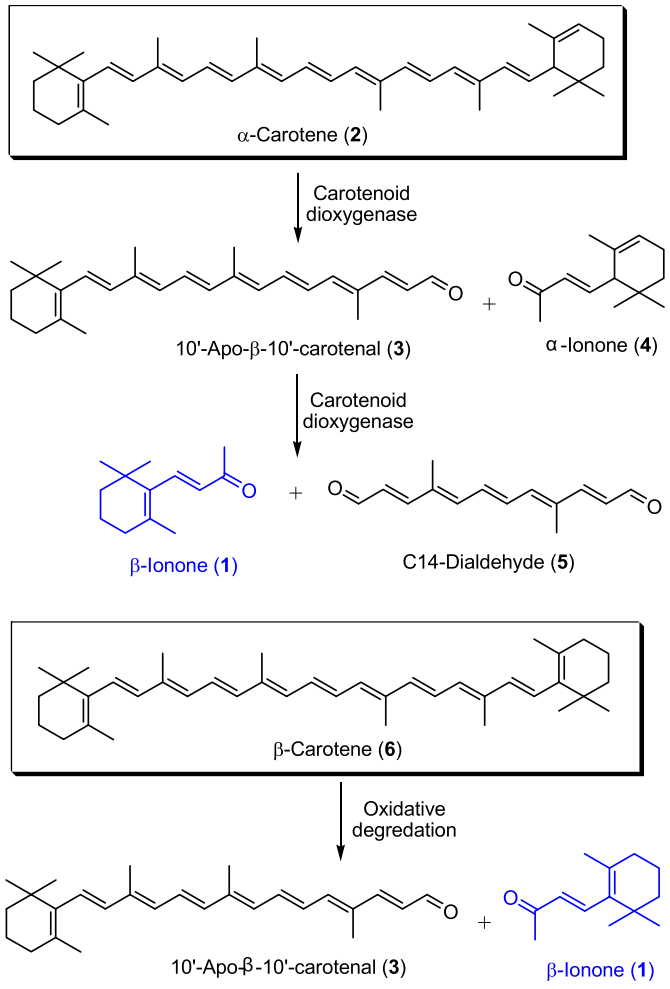


Fig. 2. Production of β-ionone from carotenes.

absorbed after oral exposure. Metabolism occurs mainly in the liver and its metabolites are 3-oxo-ionone (**7**), 3-oxo-ionol (**8**), dihydro-3-oxo-ionol (**9**) and 3-hydroxy-ionol (**10**) (Fig. 3) which were recognized in the urine of exposed rabbits [19].

3. Chemistry and reactivity of β-ionone

Several synthetic procedures were reported for the preparation of β-ionone. Cyclization of pseudoionone (**11**) is the most common method to prepare β-ionone that occurs in an inert solvent medium and in the presence of strong acids (Fig. 4) [20,21]. As seen in Fig 4, the cyclization reaction of pseudoionone (**11**) results in formation of α- and β-isomers. The composition of the resulting ionone mixture depends on the reaction conditions [22]. The high yield of β-ionone is obtained by using excess of sulfuric acid. Markovich et al. [9] reported that pseudoionone (**11**) can completely converted to β-ionone by using a mixture of trifluoroacetic acid and fluorosulfonic acid (Fig. 4).

β-Ionone and its derivatives are important intermediates with a trimethylcyclohexane scaffold which can be used as building block in the design and synthesis of ionone-derived anticancer agents. The main key reactions of β-ionone are illustrated in Fig. 5. The reactivity of β-ionone is related to the presence of carbonyl group and conjugated double bonds in this molecule. The major types of the reactions which can be used for diversification of β-ionone analogs are summarized as follows: