Critical Reviews in Oncology/Hematology 115 (2017) 27–35

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Mechanism behind the anti-tumour potential of saffron (*Crocus sativus* L.): The molecular perspective

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Contents

ARTICLE INFO

Article history:
Received 3 May 2016
Received in revised form 15 April 2017
Accepted 26 April 2017

Keywords:
Saffron
Anti-tumor
Carotenoids

ABSTRACT

Cancer is a disorder which has noted a significant rise in incidence worldwide and continues to be the largest cause of mortality. It has a dramatic impact on human life expectancy and quality of life in spite of the increase in technology and the treatments available for cancer patients. These new therapeutic options being chemotherapy, radiotherapy, photolytic therapy and catalytic therapy are known to have many adverse reactions and also no better positive outcomes than before. Hence, research is now focused more on utilizing the

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http://dx.doi.org/10.1016/j.critrevonc.2017.04.010

Crocin
Crocetin
Safranal

vast repertoire of traditional medicinal knowledge i.e. the use of flora for treatment of cancer rather than the use of chemicals. One such herb is the *Crocus sativus* L., commonly known as Saffron, rich in carotenoids – crocin, crocetin and safranal. Various studies have been carried out over the past few years to confirm the anti-cancer properties of saffron, both *in vivo* using animal models and *in vitro* using human malignant cell lines on various types of cancers with positive results. The proposed mechanism of actions has also been worked upon. This review is aimed to provide a brief overview on the anti-tumor potential of saffron focusing on the molecular mechanism involved.

1. Introduction

1.1. Overview of cancer, various chemopreventive agents and their limitations

Cancer in simple terms in the abnormal growth of cells that spread and metastasize to more distant parts from the origin through uncontrolled cell division (Chavan et al., 2013). It is one of the major non-communicable disorder, poses a severe threat to life in both developed and developing countries, due to a constant rise in incidence rate and claiming millions of lives each year (Bhandari, 2015). The impact cancer has on the health of patients depends on the age of onset, response to treatment and invasiveness (Samarghandian and Borji, 2014). Chemoprevention, the use of synthetic or natural agents or their combination, is the most widely used therapeutic option to block cancer development (Chermahini et al., 2010) apart from other emerging procedures like radiotherapy, photodynamic therapy, catalytic therapy and surgical intervention in some cases (Samarghandian and Borji, 2014; Zhang et al., 2013). Research is carried out at pharmaceutical and molecular level to understand the molecular signalling involved in cancer development as a probable target for therapy (Bhandari, 2015) and yet no success has been found to revert the disease outcome (Samarghandian and Borji, 2014). This time-limited and non-curative efficacy with severe side effects has led scientists to explore new options for cancer treatment that are safer and superior to the present conventional drugs. They have been exploiting the natural resources – herbs, vegetables, edible fruits and spices to isolate components possessing cytotoxic properties and having a potential for cancer treatment, reducing incidence and invasiveness (Bhandari, 2015; Samarghandian and Borji, 2014; Chermahini et al., 2010; Zhang et al., 2013). There are evidences that prove superiority of natural remedies to conventional therapies in terms of toxicity as well as cost (Zhang et al., 2013). There are a more than 100 plant species whose extracts have anti-cancer properties, of which some of them are *Digitalis pururea* (digitalin), *Catharanthus roseus* (vincristin, vinblastin), *Taxus brevifolia* (Taxanes), *Emblica officinalis* (ellagic acid), *Curcuma longa* (curcumin), *Solanum nigrum* (solanin), *Withania somnifera* (Withanolides), *Zingiber officinale* (curcumin), *Nigella sativa* (Thymoquinone), etc (Chavan et al., 2013). Among spices, saffron has shown positive results for numerous beneficial properties including anti-mutagenic, radical scavanging and immuno-modulting effects both *in vitro* and *in vivo*, the first anti-cancer property reported in the 1990s (Bhandari, 2015; Samarghandian and Borji, 2014).

1.2. Crocus sativus: as an important chemopreventive drug

Crocus sativus L. of Iridaceae family is a herbaceous perennial plant (Champalal et al., 2011), widely cultivated in Azerbaijan, China, Egypt, France, Greece, India, Iran, Israel, Italy, Mexico, Morocco, Spain and Turkey (Kumar et al., 2011). Commonly known as Saffron, it is the dehydrated red stigma of the flower used traditionally as a spice for flavour enhancement and food preservative (Kyriakoudi et al., 2015). The main components of saffron are crocin, crocetin, picrocrocin, and safranal, many non-volatile constituents of which most of them are carotenoids – α- and β- carotene, lycopene and zeaxanthin (Srivastava et al., 2010) which are responsible for its varied pharmacological activities. They being anticonvulsant, antidepressant, antigenotoxic, antihypertensive, anti-inflammatory, antinociceptive, antioxidant, antitussive, anxiolytic, aphrodisiac, cytotoxic or anti-cancer, relaxant activity, improves memory and learning skills, increases blood flow in retina. It can be used in crush injury, spinal cord injury, myocardial injury, neuronal injury, menstruation distress, erectile dysfucntion, lung inflammation, arthritis and parkinsonism (Champalal et al., 2011; Kumar et al., 2011; Kyriakoudi et al., 2015; Srivastava et al., 2010; Malathi et al., 2014; Akowuah and Htar, 2014; Wani et al., 2011; Hamidpour et al., 2013).It has also been found that these beneficial effects of saffron occurs at edible doses with very low or almost nil toxicity to normal cells proved by the no effect on the haematological and biochemical parameters after treatment with saffron extract (Srivastava et al., 2010; Hamidpour et al., 2013). This review focuses on the molecular and chemopreventive potential of saffron extract and its various components in cancer.

2. Mechanism of action of saffron carotenoids in cancer prevention

Literature evidences reveal that the aqueous and ethanolic extract of *Crocus* stigmas exhibit chemopreventive activity through apoptosis, anti-oxidant activity, immune modulation, enhancement of cell differentiation, inhibition of cell proliferation, modulation of carcinogen metabolism, regulation of cell growth and cell cycle progression and stimulation of cell-to-cell gap junction communication. Based on this the different hypothesis proposed are a) the inhibitory effect on DNA and RNA synthesis by interacting with DNA and causing conformational changes; b) the inhibitory effect on histone DNA complex formation; c) cell cycle arrest through p53 dependent and independent mechanisms causing apoptosis; d) interaction of carotenoids with topoisomerase II, an enzyme responsible for DNA-protein interaction (Feizzadeh et al., 2008; García-Olmo et al., 1999; Bolhassani et al., 2014; Nair et al., 1995; Bajbouj et al., 2012). By the mechanisms as stated in Table 1, saffron acts against various types of cancer; evidenced by a pool of studies conducted through the past decades, both *in vivo* and *in vitro* with promising results.

2.1. Induction of apoptosis and cell cycle arrest in cancer cells

2.1.1. Apoptosis

Apoptosis or programmed cell death is the most probable target of saffron carotenoids as determined by flow cytometry using PI staining of DNA fragmentation, characteristic for apoptotic cell death (Samarghandian et al., 2011; Tavakkol-Afshari et al., 2008). Formation of DNA fragmentation is considered to be a biological hallmark for apoptosis, presented as a typical ladder of DNA frag-