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Review

A comprehensive review of the pharmacological potential of *Crocus sativus* and its bioactive apocarotenoids

Syed Imran Bukhari*, Mahreen Manzoor, M.K. Dhar

School of Biotechnology, University of Jammu, Jammu, 180006, India

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ABSTRACT

Crocus sativus is an herbaceous plant that belongs to family Iridaceae. It is commonly known as saffron and has been used for medicinal purposes since many centuries in India and other parts of the world. Saffron of commercial importance comprises of dried stigmas of the plant and is rich in flavonoids, vitamins, and carotenoids. Carotenoids represent the main components of saffron and their cleavage results in the formation of apocarotenoids such as crocin, picrocrocin, and safranal. Studies conducted during the past two decades have revealed the immense therapeutic potential of saffron. Most of the therapeutic properties are due to the presence of unique apocarotenoids having strong free radical scavenging activity. The mode of action of these apocarotenoids could be: modulatory effects on detoxifying enzymes involved in combating oxidative stress, decreasing telomerase activity, increased the proapoptotic effect, inhibition of DNA, RNA and protein synthesis, and by a strong binding capacity of crocetin with tRNA. The present review focuses on the therapeutic role of saffron and its bio oxidative cleavage products and also highlights the possible molecular mechanism of action. The findings reported in this review describes the wide range of applications of saffron and attributes its free radical scavenging nature the main property which makes this spice a potent chemotherapeutic agent for the treatment of various diseases.

1. Introduction

Crocus belongs to family iridaceae comprising of genera and more than 85 species. *Crocus sativus* is the most important species as its dried stigmas constitute the saffron of commerce. Cultivation of *C. sativus* requires intensive labour and time thereby making it a highly priced spice [1]. Saffron has been in cultivation for many centuries and is presently being cultivated in various parts of the world namely Iran, India, Spain, Greece and Turkey. Growing pharmacological applications have increased the demand of saffron. The increasing demand in the world market is considerd to be the main reason for the expansion of saffron cultivation in other parts of the world.

The main constituents of saffron are carotenoids, glycosides, monoterpenes, aldehydes, anthocyanins, flavonoids, vitamins (especially riboflavin and thiamine), amino acids, proteins, starch, mineral matter, and gums [2]. However, among all these components apocarotenoids such as crocetin, crocin, safranal (the bio-oxidative cleavage products of zeaxanthin) and picrocrocin are considered to be the important bioactive components. Crocin is responsible for intense colour, safranal for odour and picrocrocin for bitter taste. It is mainly because of these components that saffron has gained importance as a therapeutic herb. Crocin (digentiobiosyl8, 8′-diapocarotene-8, 8′-oate; $C_{44}H_{64}O_{24}$), a diester of gentiobiose (disaccharide) and dicarboxylic acid crocetin is considered to be one of the few naturally occurring water soluble carotenoids. The flavouring property of saffron is due to the bitter glycoside, picrocrocin, 4-(β-D-glucopyranosyloxy) −2, 6, 6-trimethylcyclohex- 1- ene- 1- carboxaldehyde. ($C_{16}H_{26}O_7$). Crocin family also includes various glycosyl esters. Glycosylated forms of crocetin i.e. transcrocin-3 and trancrocin-4 are considered to be the abundant forms [3]. Most of the crocin derivatives except crocin-1 are considered to exist in cis- *trans* isomeric forms. Crocetin is the other bioactive constituent of saffron and is insoluble in water and most organic solvents. It is a natural carotenoid dicarboxylic acid. Glucosyl ester of crocetin consists of seven conjugated double bonds and four side chain methyl groups. End groups are esterified with one, two or three glucose units [4]. Earlier reports supported the existence of only six glycosides of crocetin in saffron [5]. However, more crocetin esters and their trans and cis isomers were isolated by using HPLC with UV/vis photodiode array along with spectrometry [4].

Safranal ($C_{10}H_{14}O_7$) is the main component responsible for the

Abbreviations: CSE, *Crocus sativus* extract; ROS, reactive oxygen species; DPPH, DPPH(2,2-diphenyl-1-picrylhydrazyl); GPx, glutathione peroxidase; GSH, glutathione; MDA, malondialdehyde; SOD, superoxide dismutase; LDL, low density lipoproteins; HPLC, high performance liquid chromatography

* Corresponding author.
E-mail address: syedconscious@gmail.com (S.I. Bukhari).

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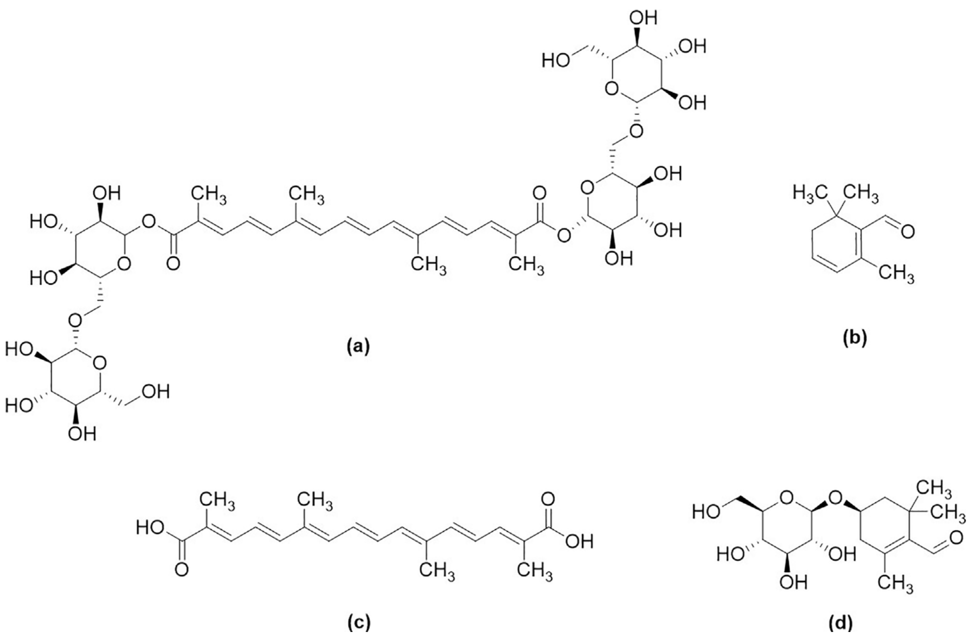

Fig. 1. Structures of (a) Crocin (b) Crocetin (c) Safranal and (d) Picrocrocin.

aroma of saffron and accounts for 60–70% of volatile fraction of saffron [6]. It is a cyclic terpenic aldehyde obtained from picrocrocin and HTCC (4-hydroxy-2, 6, 6-trimethyl-1-cyclohexen-1-carboxaldehyde) during saffron drying process [7] and is considered to be the enzymatic and thermal degradation product during storage process [8]. The structures of saffron components are illustrated in Fig. 1.

2. Therapeutic properties of saffron and its constituents

Saffron has been used in folk medicine as anti spasmodic, eupeptic, to treat menstrual cramps, lumbar pain, cough, broncial spasms, asthma, heart disease, small pox, scarlet fever and colds [9]. During the past two decades the degradative products of carotenoids have gained importance in the modern pharmacological studies and have shown several properties including anti-inflammatory, anti-tumour [10,11] anti-oxidant [11], anxiolytic [12], neuron protection and anti-neuro-degenerative disease [13–16]. Fig. 2 summarises the pharmacological application of saffron and its components.

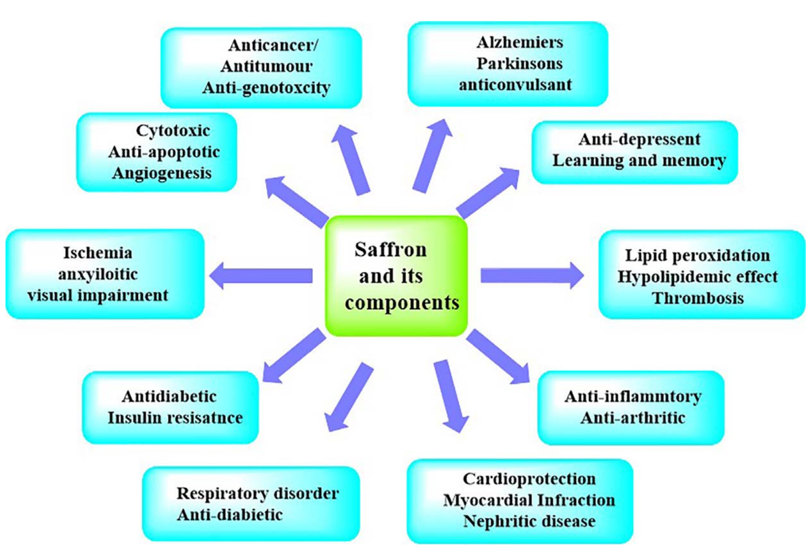

Fig. 2. Pharmacological applications of saffron and its components.

2.1. Free radical scavenging activity

In normal cells, generation of reactive oxygen species (ROS) is a normal process however, uncontrolled generation and concomitant increase of ROS level in the body results in "oxidative stress" which is considered to be the main cause of various diseases [14]. Carotenoids are known to be very efficient physical and chemical quenchers of singlet oxygen, as well as potent scavengers of ROS [3–5].

2.1.1. Saffron extract

Researches have shown that spices containing phenolic and flavonoid compounds have antioxidant activities and are frequently used as antioxidant food supplements [17,18]. The antioxidant property of *C. sativus* could be attributed mainly to its active ingredients such as safranal, crocin, crocetin and carotene, all of which have been reported to have antioxidant properties [16]. Various *in vivo* and *in vitro* studies showed the pharmacological and biological effects of saffron especially of its alcoholic extracts are predominantly because of its antioxidant potential which is considered to be the result of synergistic antioxidant potential of all the bioactive components of saffron. Martinez-Tome et al. [17] reported that saffron extract has significantly scavenged