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Original Research Article

# Wonders of "Yellow Gold" in Oral Lichen Planus

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**Abstract:** Crocus sativus, also known as "yellow gold," is a plant that is cultivated in countries such as Iran, India, and Greece. It is made up of dried red stigma and contains over 150 volatile compounds that are responsible for its aroma, including terpenes, terpene alcohol, and their esters. Two of its components, picrocrocin and safranal, contribute to its bitter taste and hay-like fragrance. This plant has several medicinal properties, including antioxidant, anti-tumorogenic, anti-inflammatory, and antidepressant effects, which make it effective in managing Oral Lichen Planus (OLP). A search of scientific journals was conducted to identify relevant articles on the potential use of crocus sativus in treating OLP. The literature suggests that crocus sativus can be used to successfully treat OLP, but more clinical studies are needed to establish its efficacy. The pharmacological properties of saffron, especially its crocin and safranal components, make it a potential therapeutic agent for various diseases, including cancer and oxidative stress. However, further laboratory-based research and clinical trials are needed to determine the precise mechanisms of action and establish its role as a novel therapeutic agent in OLP.

**Keywords:** *Crocus sativus*, Oral Lichen Planus, Anti-cancer, Antioxidant Introduction and Background.



## INTRODUCTION

The use of herbal medicines in modern medicine, particularly in oral medicine, is not a new idea. C. sativus, or saffron, is an excellent source of medicinal properties and has been used for various medical conditions, from chronic pain to serious cancers. Saffron is currently being used to treat a variety of disorders such as cramps, asthma, bronchospasms, menstrual disorders, liver disease, and pain. The purpose of this paper is to introduce the innovative idea of using saffron as a therapeutic agent for Oral Lichen Planus (OLP).

## METHODOLOGY

A search of scientific electronic databases, including PubMed Central, Science Direct, Wiley Online Library, Springer, and Google Scholar, was conducted using keywords such as "Crocus sativus," "Basics of Crocus sativus," "Anti-cancer activity of crocus," "Antioxidant activity of crocus," "Immunomodulatory activity of crocus," "Antibacterial activity of crocus," "Antidepressant activity of crocus," and "Anti-inflammatory activity of crocus" up to December 2022.

### Oral lichen planus (OLP)

Oral Lichen Planus (OLP) is a chronic mucocutaneous disorder that is mediated by autoimmune mechanisms. Its prevalence varies across different age groups worldwide. Clinically, OLP is characterized by multifocal lesions that are bilaterally present in the oral cavity. The most commonly affected areas are the buccal mucosa, lateral surface of the tongue, and gingiva. OLP can present in different forms, including reticular, popular, plaque-like, bullous, and atrophic. Current treatment guidelines aim to reduce inflammation, suppress the immune system, and eliminate the underlying cause of the condition.

### Saffron's origin

The earliest known record of saffron cultivation dates back to around 2300 BC. Sargon, the founder of the Aceadian empire, was born in a village on the Euphrates River called Azupirano, which is believed to have been a saffron-producing town (Figure 1). The saffron crocus was definitively identified in a fresco painting at the Palace of Minos in Knossos, Crete, dating from around 1700-1600 BC. The wild precursor of domesticated saffron crocus was *Crocus cartwrightianus*. Experts believe that saffron was first

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documented in a 7th-century BC Assyrian botanical reference compiled under Ashurbanipal.

Although the saffron crocus was widespread in early times, its origin has been a topic of debate for centuries in terms of location, time period, and the contribution of parent species. By comparing ancient art with modern genetics, we have found consistent results. Historians have identified *C. sativus, C. cartwrightianus, or C. haussknechtii* as the species most likely depicted in ancient art from various regions such as Iran, Greece, and Egypt. Notably, flowers shown in Aegean Bronze Age frescoes were classified by archaeologists and (paleo-)botanists as either C. sativus or *C. cartwrightianus*, indicating that at least one of these species was present in what is now Greece and providing early evidence of cultivation and economic importance. For instance, the "Adorants" fresco from Xeste 3 shows crocus flowers in great detail, with the characteristic dark-red stigmas protruding above the flower (Figure 2). This feature is fixed in C. sativus but can also occur in the more variable *C. cartwrightianus*. Along with the clusters of flowers seen in "The Saffron Gatherers," these frescoes could even be interpreted as an artistic representation of human influence on saffron's domestication (Figure 3).

Genetic research has provided strong evidence that saffron originated from two different naturally occurring cytotypes of *C. cartwrightianus* in Greece, through autotriploidy, using GBS and multicolor cytogenetics [7-8]. As a result, despite the fact that 90% of saffron is grown in Iran [9], the majority of evidence suggests that it originated in ancient Greece. To further investigate these findings, plant remains from the ancient Aegean Bronze Age would be required to confirm these hypotheses - for species identification and specifically to serve as a template for comparative ancient DNA genomics.

**Saffron's production**

The saffron plant is in the form of a leaf from October to May and blooms in October. Its flowers are hermaphroditic, meaning they have both male and female reproductive organs, and are pollinated by bees and butterflies. The plant thrives in light (sandy) and medium (loamy) soils that are well-drained and can even grow in soil that is low in nutrients. The flower has three stigmas, which are the distal ends of the plant's carpels (Figure 4). These stigmas, along with the style - the stalk that connects them to the rest of the plant - are often dried and used as a seasoning and coloring agent in cooking. Saffron blooms only once a year and must be harvested within a short time frame during a 3-4 week period in October-November. The labor-intensive cultivation process contributes significantly to saffron's high price. Some reports indicate that this species is a sterile triploid that does not produce fertile seeds. Germination can take 1-6 months at 18°C [10], and it takes three years for plants grown from seed to flower.

**Saffron's chief constituents**

The value of saffron (stigmas of *C. sativus* L.) is determined by the existence of four main secondary metabolites: crocin, crocetein, picrocrocin, and safranal [11] [Figure 5].

**Potential properties of saffron in confluence with current treatment goals of olp**

Saffron has potential properties that align with current treatment goals for OLP. These include:

1. Anti-inflammatory properties: Saffron extracts have been shown to have anti-inflammatory properties, primarily due to crocin and crocetins [12]. These extracts were effective in reducing pro-inflammatory cytokines such as NO, TNF-a, and Il-b levels in cultured microglia cells stimulated by lipopolysaccharide, a potent pro-inflammatory agent [13].
2. Antioxidant property: Saffron's antioxidant properties are mainly due to crocin, one of its carotenoid components [14-15]. The most abundant carotenoid glycoside in saffron is a-crocin or crocin-1 (C44H64O24, trans-crocetin di-(b-d-gentiobiosyl) ester), a diester formed from the disaccharide gentiobiose and the dicarboxylic acid crocetin [16]. Studies have shown that chronic treatment with saffron reduced levels of glutathione, superoxide dismutase (SOD), and catalase (CAT) [17]. Increased activity of SOD and glutathione peroxidase (GPx) has been linked to the administration of crocin. Additionally, treatment with crocin has been reported to reduce malondialdehyde content in the ischemic cortex of rats [17]. Saffron is known to scavenge cellular reactive oxygen species (ROS) [18]. Linardaki *et al.* (2013) reported that saffron extracts reversed monoamine oxidase activity and lipid peroxidation levels when co-administered with aluminum [19].
3. Anti-carcinogenic Effects: Anti-tumor effects have been demonstrated in various cellular models and extensively reviewed [20]. Saffron had selective cytotoxic effects on malignant cells, including human cancer cell lines, with effective doses in the low micromolar range while leaving healthy cells unaffected. Several hypotheses have been proposed for the modes of anti-carcinogenic action of saffron and its components. One mechanism is the inhibitory effect on cellular DNA and RNA synthesis but not on protein synthesis [20-23]. Inhibition of RNA and DNA synthesis is one of the proposed mechanisms by which crocin exerts its anti-carcinogenic activity. Sun et al. (2011) observed that 0.4 mM of crocin could downregulate the cellular RNA and DNA content of the tongue squamous carcinoma cell line Tca8113 [24]. They also observed that crocin could induce both early and late apoptosis of the cell line.

Saffron has a dose-dependent inhibitory effect on tumor cell colony formation capability while leaving normal cells unaffected [25]. Crocetin also exhibits chemopreventive activity in neoplastic cells by inhibiting RNA, DNA, and protein synthesis as well as RNA polymerase II. It also inhibits histone H1 and H1-DNA structure interaction [26].

A second suggested mechanism for saffron's anti-tumor action is its inhibitory effect on free radical chain reactions because most carotenoids are lipid-soluble and may act as high-efficiency free radical scavengers associated with membranes, which is related to their antioxidant properties [27-32].

A third proposed mechanism is that saffron extract exerts its anti-tumor effect through the metabolic conversion of naturally occurring carotenoids to retinoids. However, it was recently reported that converting carotenoids to vitamin A is not a prerequisite for anti-cancer activity [33-34].

A fourth suggested mechanism is that saffron's cytotoxic effect is associated with carotenoids' interaction with topoisomerase II, an enzyme involved in cellular DNA-protein interaction [20,35,36].

4. Immunomodulatory effect: Saffron has been shown to improve the immune system by increasing IgG levels and decreasing IgM levels [37]. It has also been found to regulate immune reactivity by inhibiting histamine (H1) and muscarine receptors [38].
5. Antidepressive effects: Saffron is a valuable tool in the fight against depression and anxiety. Safranal and crocin contribute to its antidepressant effect, with crocin likely acting via reuptake inhibition of dopamine and norepinephrine and safranal via serotonin reuptake inhibition [39]. In vitro, crocin was found to have a weak but significant affinity for the NMDA receptor and to antagonize ethanol-induced depression via the NMDA receptor [40]. Additionally, cAMP response element binding protein (CREB) is a transcription factor activated by phosphorylation at a specific serine residue. CREB regulates the neurotrophic factor brain-derived neurotrophic factor (BDNF), a key molecule targeted in antidepressant treatment. BDNF is known to decrease depressive conditions. The protein level of phosphorylated CREB increased in mice treated with saffron [41-42]. Phosphorylated CREB then increases the level of BDNF. Saffron extracts have also been found to decrease the Hamilton depression rating scale by about 10%-14% [43].

**Toxicology and safety**

"Saffron is considered safe in daily doses up to 1.5 grams. The effective dose for its properties is around 30 milligrams, leaving a large safety margin. Toxic effects have been reported at doses of 5 grams and above, with a lethal dose of approximately 20 grams [44].

**Proposal for formulation**

Saffron can be formulated into tablets, lozenges, and ointments containing active medication. Further research is needed to explore the potential use of saffron extract and its main constituents, crocin and safranal, as natural alternatives for treating OLP."

# CONCLUSION

"Saffron has been used for centuries as a spice and traditional herb and has recently gained importance in the pharmaceutical and clinical fields. While its mechanism of action in OLP is not fully understood, ongoing research suggests that saffron may have potential as a therapeutic agent against the progression of OLP cancer. However, more evidence and extensive research are needed to confirm its use as a novel treatment for OLP."

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