





Review

The Multifaceted Therapeutic Potential of Saffron: An Overview Based on Research and Patents

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Abstract: Plants and plant extracts have long been acknowledged as valuable resources for the development of therapeutic formulations for various diseases. Among them, numerous plants and plant-derived products have demonstrated cytotoxic and/or anti-tumor properties. Saffron, particularly due to its major compounds, namely crocin, crocetin, and safranal, stands out as a promising candidate in this regard. Our research undertakes a literature review, reaffirming the antioxidant, anti-inflammatory, and, notably, anti-tumor properties of saffron and its major constituents. Additionally, this study examines relevant patent documents, highlighting innovative applications for saffron and its major compounds in cancer therapy. The review discusses the progress in purifying the compounds extracted from saffron and assesses their impact on cytotoxic trial outcomes, the potential synergies between certain saffron compounds and established cytotoxic molecules, and the limitations of the patents examined, particularly concerning reported clinical evidence. Researchers who focus on advances in oncology will know from our findings the evolution of the patent landscape regarding cytotoxic and/or anti-tumor therapeutic applications using saffron or its main compounds. Moreover, investigators can draw inspiration from patents leveraging traditional knowledge, particularly from Chinese medicine, to clarify specific active molecules and their mechanisms of action and can expedite the translation of these findings into clinically relevant interventions, potentially enhancing cancer therapy outcomes.

Keywords: saffron; anti-tumor; crocin; crocetin; safranal; patent

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1. Introduction

Natural products have played a crucial role in drug discovery throughout history, offering a rich source for developing new drugs with diverse medicinal properties [1–3]. These compounds have been extensively studied in various fields, such as pharmacology, cosmetics, and medicine, due to their significant antioxidant, anti-inflammatory, cytotoxic, and anti-tumor activities [4–8]. The exploration of natural plants for their therapeutic potential, particularly in cancer treatment, remains a prominent challenge in modern times, with a focus on developing effective drugs to combat tumors and cancer [9]. The complex and diverse chemical structures of natural products offer promising avenues for the prevention and treatment of diseases, highlighting their importance in addressing critical health issues like cancer [10].

Saffron (*Crocus sativus* L.) stands out as a valuable natural product rich in both primary and secondary metabolites [11]. Considered the world's most expensive spice, it offers different chemical and biological properties that allow a wide array of therapeutic benefits [12]. Saffron and its bioactive constituents, including crocin, crocetin, and safranal, indeed showcase a diverse range of therapeutic properties [13]. These compounds exhibit potent antioxidant and radical scavenging activities due to their phenolic and flavonoid

contents [14]. These activities could effectively inhibit free radical oxidation and potentially prevent skin tumors, aging, and other diseases [15]. Moreover, saffron extracts display significant anti-inflammatory effects by reducing neutrophil infiltration, inflammatory pain responses, and levels of inflammatory mediators like histamine through immunomodulatory pathways [16]. Importantly, saffron demonstrates selective cytotoxicity against cancer cells while preserving normal cells, inducing apoptosis and inhibiting cell proliferation, DNA/RNA synthesis, and topoisomerase activity in malignant cells through diverse mechanisms such as gene expression modulation and inhibition of metalloproteinases and urokinases [17]. Specific derived compounds exhibit promising anti-cancer effects against various cancer types, positioning saffron as a potential candidate for cancer prevention and therapy pending further clinical validation [18].

Saffron, known as the red gold in producer countries, belongs to the Iridaceae family [19]. The origin of the word saffron is the Arabic name “Azaferan”, a word that means “yellow”. The word *Crocus* is of Greek origin [20]. It grows in Iran, Greece, India, and several places in the Mediterranean region (France, Italy, Spain, Morocco, Egypt, Turkey, etc.), as well as in Switzerland, Pakistan, China, the United Arab Emirates, Japan, and Australia [21]. Because of its unique odor and color, saffron is used as a coloring agent in foods and cosmetics. Saffron is known for its colored flowers, which have three long (25–30 mm) stigmas drooping over the tepals [22–24]. The flowers also have three yellow stamens [19]. The growth pattern of saffron is different from other crops and can be divided into three stages: flowering, vegetative stage, and formation of corms. Flowering occurs during autumn (October through November), followed by the vegetative stage throughout winter and the formation of replacement corms at the base of the shoots [25]. Figure 1 displays images of the *Crocus sativus* plant and *Crocus* stigmas.



Figure 1. (A) Image of *Crocus sativus* plant. (B) Image of *Crocus* stigmas. The images were captured by the author, Y. R. Elfardi in 2024 at 31°38'37.1" N 6°27'44.4" W (Ait Bouguemez, Morocco).

The approximate analysis and composition of dried saffron stigmas show that part of the plant contains more than 150 components, including lipophilic and hydrophilic carbohydrates, proteins, amino acids, minerals, mucilage, starch, gums, vitamins, pigments, alkaloids, and saponins [22]. However, the oxidative degradation of the zeaxanthin precursor, after breaking, gives rise to crocin, crocetin, and safranal, the major components of saffron stigmas, as shown in Figure 2.

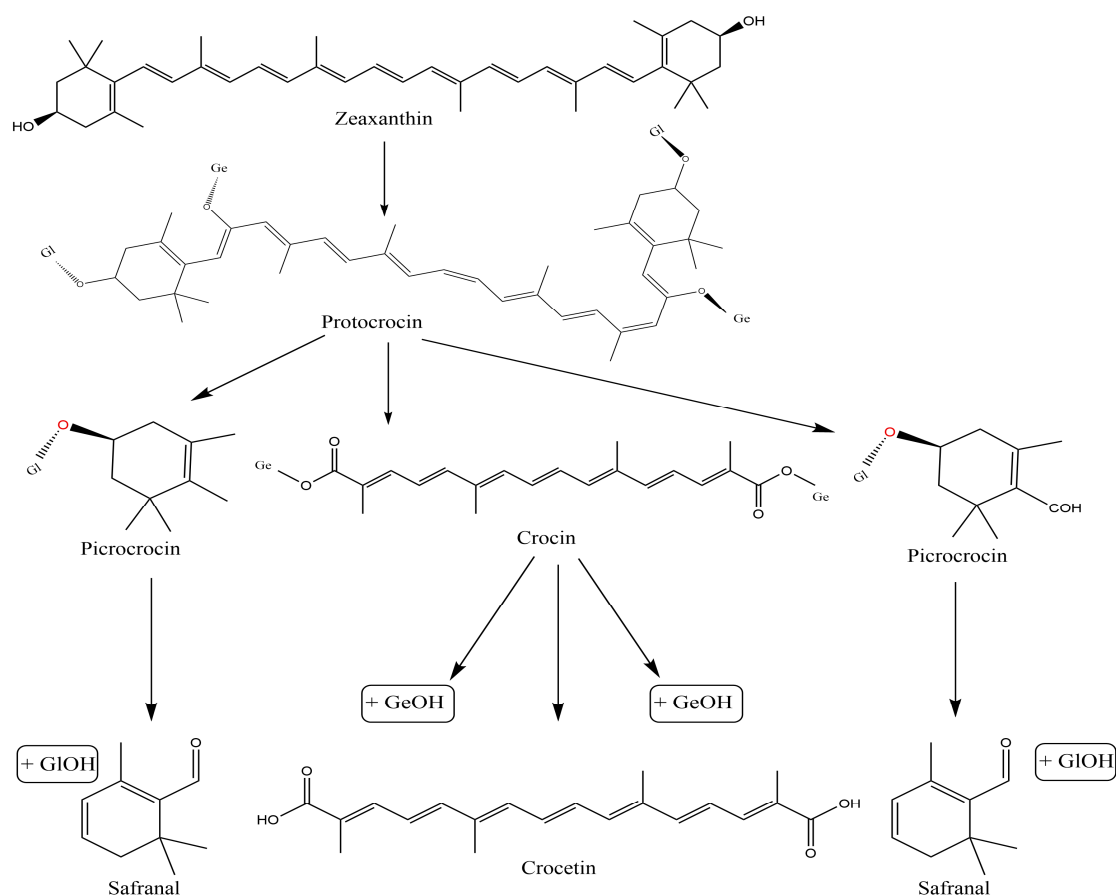


Figure 2. The biosynthetic pathways and the relationship between the key compounds in saffron stigmas based on the biosynthetic pathways: [Zeaxanthin → Picrocrocin → Safranal + D-Glucose (GIOH)] and [Zeaxanthin → Crocetin → Crocin (Crocetin + Gentiobiose (GeOH))]. Adapted from Shahi et al., 2016 [22], with permission from Elsevier; published under license, Copyright© 2016 Elsevier Ltd.

The key bioactive compounds are all derived from the carotenoid precursor zeaxanthin through different biosynthetic pathways during the development and drying process of saffron stigmas [26,27]. Briefly, zeaxanthin undergoes oxidative cleavage by the enzyme carotenoid cleavage dioxygenase to form the apocarotenoid crocetin dialdehyde, which is subsequently converted to crocetin ($C_{20}H_{24}O_4$) by an aldehyde dehydrogenase [27–29]. Crocetin then follows two parallel pathways:

1. Crocetin is glucosylated by glucosyltransferases to form crocins (crocetin glycosides), primarily crocin-4, by the addition of gentiobiose (GeOH: $C_{12}H_{22}O_{11}$), a disaccharide of two glucose units [27–29]. In summary: Crocetin + GeOH → Crocin.
2. Zeaxanthin is also converted to picrocrocin ($C_{16}H_{26}O_7$), a colorless monoterpene glycoside and precursor of the saffron aroma component, a monoterpene glycoside, through a separate pathway [28,29]. During the drying and processing of saffron stigmas, the enzyme β -glucosidase acts on picrocrocin, cleaving it to release safranal ($C_{10}H_{14}O$) and D-glucose (GIOH: $C_6H_{12}O_6$) [28–30]. In summary: Picrocrocin → Safranal + GIOH.

Concerning saffron's phytochemical composition, it should be noted that it varies significantly based on planting conditions, seasons, and origin [31–33]. Different origins and harvesting years impact the crocin profiles of saffron samples [34]. Furthermore, environmental factors like solar radiation and air temperature influence the content of apocarotenoids and phenolic constituents in saffron, with variations observed across countries like Ukraine and India [35]. On the other hand, the geoclimatic characteristics of the

territory play a crucial role in determining the chemical composition of saffron, leading to distinct final products [36]. Moreover, the sensory perception of saffron is closely related to its chemical composition, with crocins, picrocrocines, and safranal being key substances that impact the quality and economic value of this highly sought-after spice [37].

In the following, we underscore the importance of saffron and its main components, especially for their antioxidant, anti-inflammatory, cytotoxicity, and anti-tumor activities. Then, we will expose the information from the patent documents in terms of developments in patentability in the studied field, as well as relevant innovative applications that benefit from the properties of saffron and its major compounds to develop cytotoxic and/or anti-tumor formulations.

2. Resources and Methods

Saffron bioactivities were compiled from research published on scientific databases, including PubMed, Web of Science, Scopus, SciFinder, Wiley Online, Science Direct, and the Cochrane Library. The main search keywords were: “saffron”, “*Crocus plant*”, “*Crocus sativus*”, “ethnopharmacology of saffron”, “antioxidant activity”, “anti-inflammatory activity”, “anti-tumor activity”, “saffron as an anti-tumor”, “pharmacological activity”, and “toxicity”. The PRISMA flow diagram of this part is presented in Figure 3A. The aim is to demonstrate how we selected the articles we reviewed and summarized hereinafter. The irrelevant studies, those with unclear data, or those that do not provide full-text access were omitted according to the exclusion criteria.

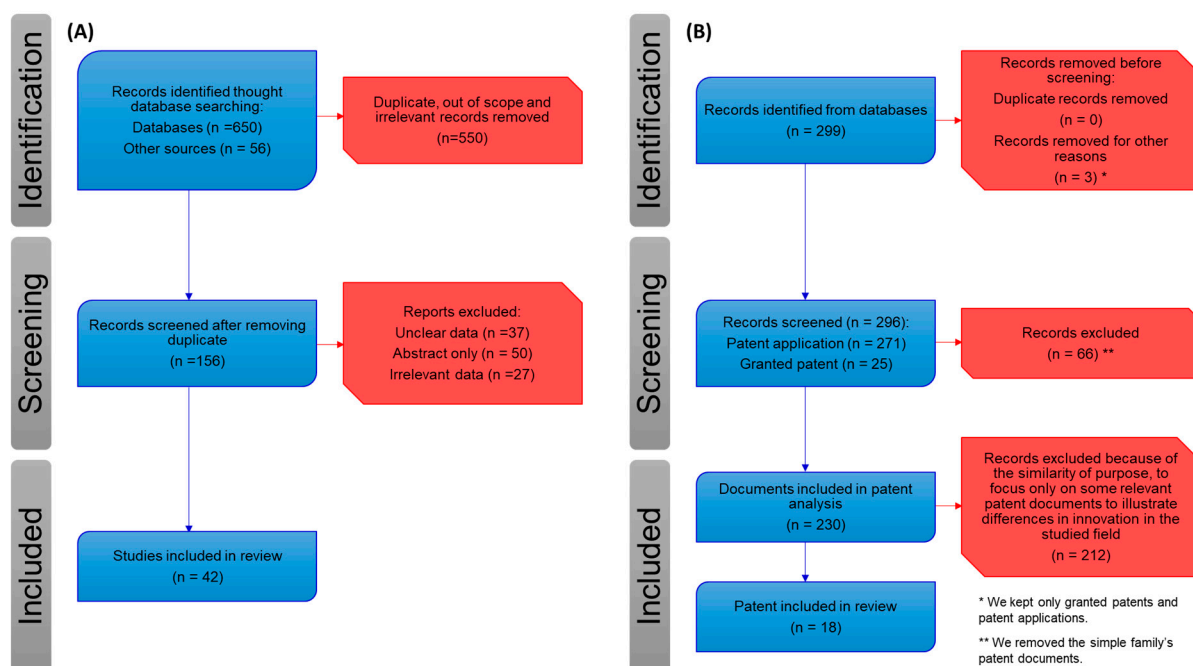


Figure 3. The PRISMA flow diagrams used for this study: (A) selected articles; (B) selected patents. The search was carried out to find either articles or patents from 1990 to the present.

On the other hand, the patent documents (i.e., patent application and granted patent) used for this study were extracted from specialized databases, namely Lens [38], Patentscope [39], and Google patents [40]. We used appropriate keywords like “saffron” and its major compounds “crocin”, “crocin”, and “safranal”, coupled with tumor-related keywords. The most relevant patents, according to the matching score used in Elasticsearch, have been reviewed. The PRISMA flow diagram of this part is presented in Figure 3B. The aim is to demonstrate how we selected the patents we analyzed and reviewed hereinafter.

3. Review of Saffron's Main Biological Activities

3.1. Antioxidant Activity

Antioxidants effectively inhibit free radical oxidation and can potentially prevent skin tumors, aging, tumors, and other diseases. Baba et al. studied the antioxidant activity of all parts of saffron (i.e., corm, leaf, and stigmas) using many certified assays, such as the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay, the nitro blue tetrazolium reduction assay, and the ferric reducing power assay. The half-maximal inhibitory concentration (IC_{50}) values for the ethanolic extracts of stigmas, corm, and leaf were 207.16, 246.22, and 482.78 $\mu\text{g/mL}$, respectively, while the IC_{50} values for aqueous extracts of stigmas and corm were found to be 304 and 465 $\mu\text{g/mL}$, respectively [15]. These results indicate that ethanolic extracts of saffron show higher antioxidant activity compared to aqueous extracts. A comparative investigation also reports that the highest antioxidant activity was presented by the ethanolic extract of stigmas, followed by corm and leaf [15]. The antioxidant activity of saffron extracts is due to the presence of secondary metabolite flavonoids, phenolics, and carotenoids in saffron. Other studies have also indicated the antioxidant properties of crocin, picrocrocine, and safranal [41–43]. Moreover, many *in vivo* studies have shown that saffron and its components exert antioxidant activity and could prevent oxidative stress [44–46]. This scientific research shows that saffron is a rich source of natural antioxidants that can potentially prevent and treat some diseases [11].

3.2. Anti-Inflammatory Activity

Saffron also has confirmed anti-inflammatory properties. The aqueous extract of saffron stigmas (i.e., crocin) has strong antioxidant properties that can inhibit the production of free radical oxygen and pro-inflammatory cytokines in treated mice [47]. In addition, the anti-inflammatory effects of saffron ethanolic extracts have been investigated using the mouse paw edema test [48]. Oral administration of saffron ethanolic extracts led to a significant decrease in edematous paw volume in a time-dependent manner. As conclusions, Khan et al. confirmed that both corm ethanolic extract and leaf ethanolic extract exhibited a mild to moderate response against inflammation in adult albino mice [48]. On the other hand, crocin was found to modulate the inflammatory process by exerting a dual inhibitory effect against the cyclooxygenase 1 and 2 enzymes, with IC_{50} values of 9.7 and 1.2 μM , respectively, compared to indomethacin used as a control, which had IC_{50} values of 2.1 and 2.8 μM , respectively [49]. Also, crocin orally administered at 25, 50, and 100 mg/kg had potent inhibitory effects on paw swelling and the production of prostaglandin E_2 (PGE_2) in a homogenate of inflamed paw prostaglandin E_2 production in male Kunming mice. It also exhibited good inhibition of xylene-induced ear edema in mice [49]. In conclusion, the anti-inflammatory effects of the extracts are attributed to their content of flavonoids, tannins, anthocyanins, and alkaloids [47,50].

3.3. Cytotoxicity Activity

According to the World Health Organization, 80% of Asian and African people use medicinal plants to conserve their health. In acute toxicity tests, Bahmani et al. reported that oral administration of an aqueous extract of saffron in mice resulted in a median lethal dose (LD_{50}) value of 4120 mg/kg [51]. In subacute toxicity tests, the intraperitoneal administration of saffron aqueous stigma extract in mice resulted in an LD_{50} value of 1.6 g/kg. Also, after administration of saffron tepal aqueous extract in mice, the LD_{50} value was 6 g/kg [52]. The ethanolic extracts of saffron orally administered showed no mortality in the adult albino mice treated [48]. Administration of crocin via intraperitoneal (IP) injection and oral administration did not lead to any mortality in mice after 48 h. Safranal was also evaluated in rats and mice using IP or oral administration [53]. The LD_{50} values of safranal were 21.42 mL/kg in male mice, 11.42 mL/kg in female mice, and 5.53 mL/kg in male rats following oral administration, while IP exposure was 1.48 mL/kg in male mice, 1.88 mL/kg in female mice, and 1.50 mL/kg in male rats. In addition, safranal decreased cholesterol, triglyceride, and alkaline phosphatase. Lactate dehydrogenase and serum urea

nitrogen were increased by safranal. Histological studies indicated that safranal did not have any toxic effects on the heart, liver, or spleen and that it could be used as a drug [54]. Based on LD₅₀ values, it can be concluded that saffron aqueous or ethanolic extracts and their components are slightly toxic and practically nontoxic in acute exposure.

3.4. Anti-Tumor Activity

Many studies show that saffron extract can inhibit tumor formation and tumor cell growth (Table 1). As an example, oral administration of 200 mg/kg of ethanolic extract of saffron can inhibit the growth of Sarcoma-180, Ehrlich ascites carcinoma (EAC), and Dalton's lymphoma ascites (DLA) tumors in mice. This dose is still high, as the LD₅₀ required to kill 50% of the animals receiving saffron extract was under 600 mg/kg body weight [55]. According to the findings of the other studies in Table 1, it was confirmed that saffron extract exhibits antimutagenic properties against various DNA-damaging agents [56,57]. Additionally, it demonstrates anti-proliferative activity against acute lymphoblastic leukemia [58]. Crocetin, a component of saffron extract, demonstrates a potent anti-tumor effect when compared to the extract itself [57,59]. Furthermore, the ethanolic extract of saffron flower showed significant inhibition of colony formation and cellular nucleic acid synthesis, with 50% inhibition at some concentrations [60]. Another study showed that an ethanolic extract of the dried stigmas of saffron could decrease cell viability in malignant cells in a concentration- and time-dependent manner, which means that saffron contains bioactive compounds that inhibit the proliferation of the human alveolar cell line (A549) with IC₅₀ values of 1200 and 650 µg/mL after 24 and 48 h, respectively [61]. This denotes that saffron could cause cell death in the A549 cells and could also be considered a promising chemotherapeutic agent in lung cancer treatment [61]. The carotenoids extracted from the stigmas of saffron, especially its derivative dimethyl-crocetin (DMCRT), induced functional terminal differentiation in the human promyelocytic leukemia cell line HL-60. The concentrations that induced 50% inhibition of cell growth were 1.2 µM for DMCRT, 5 µM for crocetin, and 6.6 µM for crocin carotenoids after 3 days of incubation [62]. The saffron aqueous extract inhibits the progression of gastric tumors in rats in a dose-dependent manner [44]. In fact, the administration of crocin alone or in combination with 5-fluorouracil vividly reduces the tumor number and tumor size in both the distal and mid-colon, followed by a reduction in the disease activity index [63]. In vivo studies of the formulation (PEGylated nanoliposomes) containing crocin extracted from saffron stigmas at doses of 50 and 100 mg/kg can decrease tumor size and increase survival rates [64]. With an IC₅₀ of 0.625–5 mg/mL, crocin inhibits the proliferation and induces the apoptosis of human leukemia HL-60 cells in vitro [65]. In vivo, crocin inhibits the tumor weight and size of HL-60 xenografts in nude mice with an IC₅₀ of 6.25–25 mg/kg [65]. The inhibition of RNA and DNA synthesis is one of the main mechanisms of the anti-tumor and anti-carcinogenic effects of saffron [66].

Table 1. In vivo anti-tumor activities of saffron extract and its active metabolites.

Part or Component	Extraction Fluid	Dose	Cell Line	Control	Target	Anti-Tumor Activities	Ref.
Saffron	Ethanol (95%)	200 mg/kg	Sarcoma 180 P388 leukemia, Ehrlich ascites carcinoma (EAC), and Dalton's lymphoma	Without drug (untreated)	Male Swiss albino mice with tumors receive drug orally, one per day	Extract inhibits the growth of tumors in mice	[55]
Dried stigmas	Water	20, 40, and 80 mg/kg	N/A	Genotoxins alone treated group)	Injected intraperitoneally in old male Swiss albino mice	Saffron extract has an antimutagenic action against different DNA-damaging agents	[56]

Table 1. Cont.

Part or Component	Extraction Fluid	Dose	Cell Line	Control	Target	Anti-Tumor Activities	Ref.
Crocetin	N/A	100 mg/kg	Tumor cell lines (U251, U87, U138, and U373)	IP injections of DMSO/PBS controls	Anti-tumor effects in models of human glioblastoma	Saffron extract has an antimutagenic action against different DNA-damaging agents	[57]
Dried stigmas	Methanol	0–500 µg/mL	<i>Jurkat</i> cells (T lymphocyte cells)	Untreated	Human acute lymphoblastic T-cell leukemia	Extract has anti-proliferative activity against acute lymphoblast leukemia	[58]
Dried ground stigmas	Aqueous + Ethanol (25 mL + 85 mL)	300 mg/kg	Prostate (PCa) cells (PC3 and 22rv1)	Untreated	Saffron extract, or crocetin, is administered to athymic nude mice five days a week	Crocetin shows a strong anti-tumor effect compared to extract	[59]
Crocetin	N/A	100 mg/kg	N/A	N/A			

N/A: not applicable.

In summary, based on cytotoxicity and anti-tumor research studies, saffron and its main components are not toxic for use as drugs against cancer. However, further clinical trials are needed to study the interaction between saffron components and enzymes in the human body to understand the mechanism of action of the extracts of saffron in curing tumors (Table 1).

4. Patents on Saffron to Prevent and Treat Tumors

4.1. Patent Analysis

Patent documents provide a detailed technical record of the history of innovation in a given field [67]. They are therefore considered an important resource to deeply understand the progress of any study [68]. In the case of the use of saffron and its bioactive constituents in the fight against tumors, we identified 296 relevant documents, including 271 patent applications and 25 granted patents (Figure 3B).

In terms of publication year, Figure 4 shows the temporal evolution of the publication of patent documents. The oldest document is a patent application published in 1995 that relates to a therapeutic formulation for esophageal cancer [69]. The claimed composition is composed of 14 components, including saffron, with 4.5 to 5.5% *w/w*. The patent in question was granted in 2000 [70]. We observe that since this first document, publications have multiplied, particularly later in 2010, confirming the potential that inventors find in saffron as an anti-tumor agent.

The patent documents each bear one or more classification codes that allow easy identification of the technical field(s) of the invention [4]. There are several types of classification, the most common of which is the International Patent Classification (IPC) [71]. According to IPCs, we observe the assignment of 15 classification codes, all belonging to sub-class A61P, relating to medicinal preparations based on the specific activity of chemical components [5]. A61P35/00 is the majority sub-group (36% of the codes assigned to the documents studied) and is related to antineoplastic treatments treating tumors, which is consistent with our research topic. Patents have a limited geographical scope, which is why it is important to identify the jurisdictions to which these patents relate. We found that China is the jurisdiction where about 60% of the documents are published. As we will see in what follows, one of the explanations for this observation is that several innovations in the fight against tumors using natural compounds have their bases in traditional Chinese medicine. The jurisdiction of the United States, followed by depositions through the global system named the Patent Cooperation Treaty (PCT), which covers several countries, come in second and third place, with about 19% and 14% of documents, respectively.

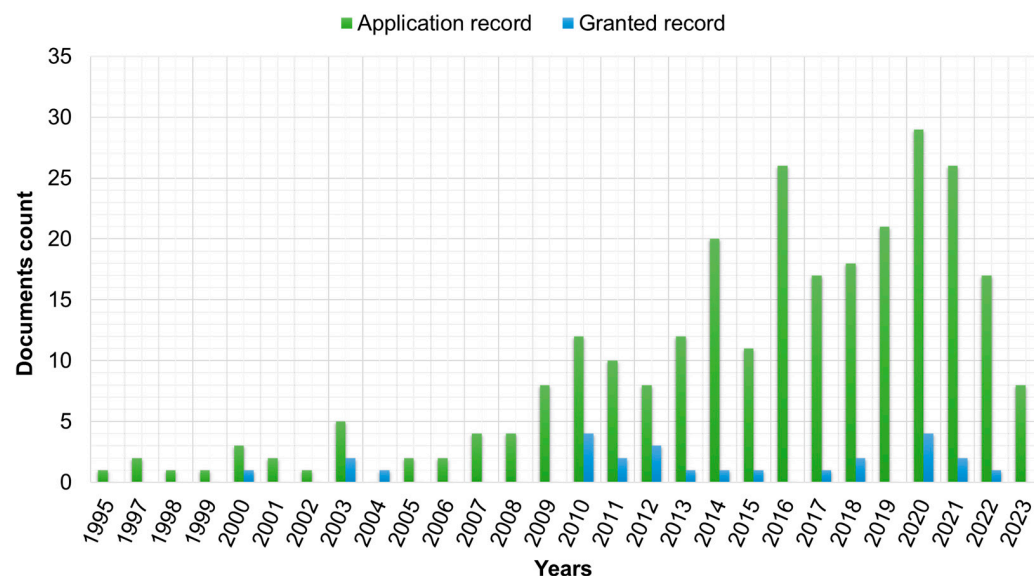


Figure 4. Evolution of patent publication records (patent applications and granted patents) on saffron as an anti-tumor agent.

4.2. Review of Relevant Patents Related to Saffron and Its Derivatives to Prevent and Treat Tumors

The first group of patents concerns the use of stigmas of saffron as a component of anti-tumor remedies based on traditional Chinese pharmacopeia; however, the second group of patents studied concerns the use of one or more major biomolecules from saffron for the formulation of anti-tumor remedies. Patents inspired by traditional Chinese medicine have some common points. Firstly, they adopt two principles to prevent and cure tumors, which are the strengthening of the body's immunity and overall resistance by nutraceutical supplements that could eliminate any possible deficiency and also the use of purifying compounds that can eliminate any microbes or chemical substances from the living environment that are likely to be pathogenic [72,73].

Then, between these patents, other common points are noted, such as a formulation based on several natural compounds and the use of stigmas of saffron without specifying the active molecule that allows the therapeutic effect. Table 2 lists the relevant patents based on Chinese medicine, the number of compounds used for the invented formulation, and the type of tumor covered by the patent, where specified [74–79].

Table 2. List of relevant granted patents using saffron as an anti-tumor agent based on Chinese medicine.

Publication Date	Title	Tumor Type	Number of Materials *	References
7 April 2010	Medicine for treating women's tumors and malignant tumors and its preparation process	Gynecological and malignant tumors	15	[74]
2 June 2010	Medicine for treating and preventing esophagus tumors and gastric tumors and the preparation method	Tumors of the esophagus and the stomach	13	[75]
13 April 2011	Medicament for adjuvant therapy of tumors and preparation method thereof	Not specified	12	[76]

Table 2. Cont.

Publication Date	Title	Tumor Type	Number of Materials *	References
8 February 2012	Chinese medicinal composition and preparation method and application thereof	Tumors of the lung, esophageal, stomach, and kidney and nasopharyngeal cancers	10	[77]
30 May 2012	Black lotus raw juice tumor preventing and treating medicament	Not specified	10	[78]
14 November 2012	Traditional Chinese medicine for treating and preventing tumors and production method thereof	Tumors of lung, breast, liver, cervix uteri, ovary, stomach, bladder, and rectum	28	[79]

* Number of materials indicates how many different raw materials were used in the invented formulation, of which saffron is a part.

These Chinese inventions are inspired by traditional medicine and adopt its terminology and concepts. Although this medicine is recognized as serious and efficient [80–82], patents do not provide sufficient proof of the validity of their inventions and most of them need more clinical investigations to rationalize those applications stimulated by traditional uses. In 2022, for example, Zhou prepared a formulation for the treatment of several types of tumors based on plants, including saffron, through aromatherapy [83]. Although it describes the targeted effects of each raw material and the relative proportions of these effects for the claimed therapeutic formulation, the clinical results are limited to three cases of patients with different tumors who observe positive effects after administration of the said composition, with a follow-up being carried out for only a few weeks. We observe this lack of clinical testing in several other patents. As examples, the granted patent CN101732551B [78] provided no test results; the granted patent CN101926895B [77] brings forth only six cases of the clinical use of an embodiment from the invented formula, with satisfying results; and the granted patent CN101693097B [76] comes up with only seven cases of the clinical use of an embodiment from the invented formula, with some satisfying results. In the granted patent CN102008651B [79], which describes 53 cases of patients using the invented therapeutic formulation, various diseases are targeted but the clinical trial protocols are not detailed. However, a few patents do describe an exhaustive and solidly constructed experimental protocol, such as the granted patent CN101091769B [75], where a clinical trial was carried out on 136 patients divided into two comparable groups in terms of sex, age, and duration of the disease. The trial leads to favorable conclusions for the treatment related to the invention, which significantly improved the health status of the patients compared to the untreated ones.

Other patents are based on the cytotoxic or anti-tumor therapeutic formulations of chemical compounds that can be extracted from saffron. In the following, we present the most relevant granted patents in this category, and we have limited ourselves to innovations using the major secondary compounds of saffron, namely crocin, crocetin, and safranal.

Jianxin et al. claimed in 2010 a method for producing crocetin through a simple chemical synthesis process, thereby reducing the reliance on saffron and meeting market demand [84]. The technical approach used 3,7-dimethyloctylenedialdehyde and methyl 2-bromopropionate as raw materials. The synthetic process given in the patent document describes reactions to produce crocetin dimethyl ester, followed by subsequent steps of hydrolysis, decolorization, and recrystallization to yield a purified crocetin. An organic solvent serves as the reaction medium, and the process is conducted in a nitrogen-protected environment with an antioxidant system [84].

Eidenberger claimed in 2013 a pharmaceutical or nutraceutical composition derived from plant (saffron or gardenia) extracts containing crocin [85]. This composition includes a hydrolysate enriched in crocetin monoesters derived from crocin during hydrolysis. The

hydrolysate is obtained through a method involving the acidic or basic hydrolysis of a crocin extract low in crocetin monoesters. The hydrolysates in this invention can be purified using chromatography, high-performance liquid chromatography, gel chromatography, crystallization, distillation, and similar techniques. Determining the specific monoester can be achieved through methods familiar to experts in the field, like chemical degradation, chromatography, and spectroscopy. The resulting composition can be applied to cosmetic, pharmaceutical, nutraceutical, or dietary supplement products, with potential therapeutic applications in treating conditions such as cancer [85].

In 2015, Gao claimed an invention designed to prevent and treat various stages of tumor development by delivering high-purity crocin and/or crocetin in composition products [86]. By purifying and enriching natural crocin and/or crocetin, the invention seeks to overcome the variability in plant (saffron or gardenia) quality and active ingredient content. The invention also permits the improvement of the therapeutic effectiveness of existing tumor drugs through synergistic effects. It acts as an enhancer, reducing drug resistance. Invention composition searches for ways to minimize collateral damage during tumor treatment by safeguarding normal cells, tissues, and organs from injury caused by anti-tumor agents and radiation. As we recapitulate in Table 3, the patent description presents some composition examples to explain and illustrate the invention compositions that offer a diverse range of health benefits, from tumor prevention and treatment to enhancing overall health, with specific formulations targeting various aspects of well-being [86].

Table 3. Some embodiments listed in the granted patent US9211298B2 (Gao, 2015 [86]).

Example	Ingredients	Purpose/Health Benefits
1	Crocina and/or Crocetin, Green Tea Extract, Curcumin, Resveratrol, Panax Ginseng Extract, α -Lipoic Acid, and L-Carnitine	Prevent or treat tumors and other diseases; improve health
2	Crocina and/or Crocetin, Green Tea Extract, Curcumin, Grape Seed Extract, Panax Ginseng Extract, Rhodiola Rosea Extract, and Ginkgo Biloba Extract	Prevent or delay tumors and neurodegenerative diseases, enhance brain health, and protect organs
3	Crocina and/or Crocetin, Dihydromyricetin, Resveratrol, and Artichoke Leaf Extract	Protect the liver from injury and alcohol damage, treat liver conditions, and prevent or treat diseases
4	Crocina and/or Crocetin, Citrus Extract, Curcumin, and Resveratrol	Prevent or treat tumors; lower the risk of diseases.
5	Crocina and/or Crocetin, Lycopene, β -Carotene, Bilberry Extract, Lutein, and Zeaxanthin	Prevent or treat age-related macular degeneration; improve eye and brain health
6	Crocina and/or Crocetin, Mannitol	Treat tumors and neurodegenerative disorders.
7	Crocina and/or Crocetin, Dihydromyricetin, Citric Acid, Sodium Bicarbonate, PEG 6000, Flavorant, and Aspartame	Protect the liver, enhance heart functions, and prevent or treat diseases
8	Crocina and/or Crocetin, Rebaudioside A, Glycyrrhizic Acid, Ammonium Salt, and Erythritol	Improve eye and brain health and prevent diseases

In 2018, Dhar and Gutheil claimed the invention of a purified crocetin that was more potent for tumor treatment than other commercial crocetins [87]. The granted patent encompasses various aspects related to the purification and fractionation of crude crocetin. It introduces a novel crocetin compound that surpasses the potency of crude crocetin by 50 times, exhibiting low toxicity. Additionally, the invention involves crocetic acid, which serves as an anti-tumor agent, demonstrating efficacy in inhibiting proliferation and stimulating apoptosis in both general tumor cells and specifically in pancreatic tumor cells [87]. Figure 5A describes a comparison of the cell proliferation of a pancreatic tumor following incubation with invented purified crocetin or crude crocetin at different

concentrations (0, 1, and 10 μM). The graph clearly shows a significant regression in the proliferation of these cells when the newly invented crocetin is used. At a concentration of 10 μM , cell proliferation is reduced by 75% in the presence of purified crocetin, whereas it is only inhibited at a percentage of 10% in the presence of raw crocetin. Figure 5B shows a comparison of the apoptosis of pancreatic tumor cells under the same conditions and concentrations as in the previous experiment. The graph shows that, at a concentration of 10 μM , the measured optical density when the invented crocetin is used in pancreatic cells is 2.5 times higher than when the crude crocetin is used. This demonstrates the increase in tumoral cell death and thus the reduction of the tumor with the purified crocetin, whereas the crude crocetin appears to be ineffective, even when increasing its concentration. The application extends to the treatment and prevention of tumors, particularly pancreatic tumors, with the purified component solely or in combination with other anti-tumor agents. The invention further covers compositions, pharmaceutical formulations, and diagnostic tools incorporating crocetin acid [87].

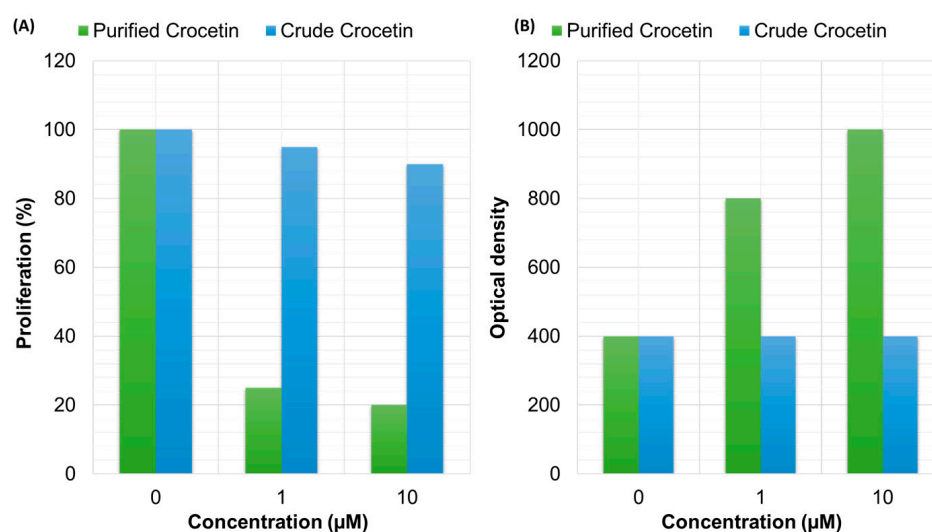


Figure 5. Action of invented crocetin compared with crude crocetin on pancreatic cancer cells provided through the granted patent US10155715B2: (A) Comparison of pancreatic cells proliferation incubated with purified or crude crocetin. (B) Comparison of pancreatic cells apoptosis incubated with purified or crude crocetin. Adapted from Dhar and Gutheil, 2018 [87] (Copyright-free figure).

More recently, teams from the United Arab Emirates University (Al Ain, United Arab Emirates) have studied liver tumors, which have a high rate of recurrence, are resistant to conventional chemotherapy, and whose side effects exhaust patients. In many cases, the treatment protocol uses sorafenib, a multikinase inhibitor that blocks tumor cell multiplication. However, this drug shows reduced efficacy in the advanced stages of liver tumors, the early stages of which are usually asymptomatic. In 2020, Amin et al. claimed a combination therapy comprising sorafenib and safranin or a pharmaceutical derivative thereof [88]. To illustrate the efficacy of the invention, the patent description presents an experimental protocol on rats, where hepatocellular carcinoma (HCC) is chemically induced by diethylnitrosamine (DEN) [88]. Figure 6 summarizes this protocol and gives the results concerning tumor nodule proliferation.

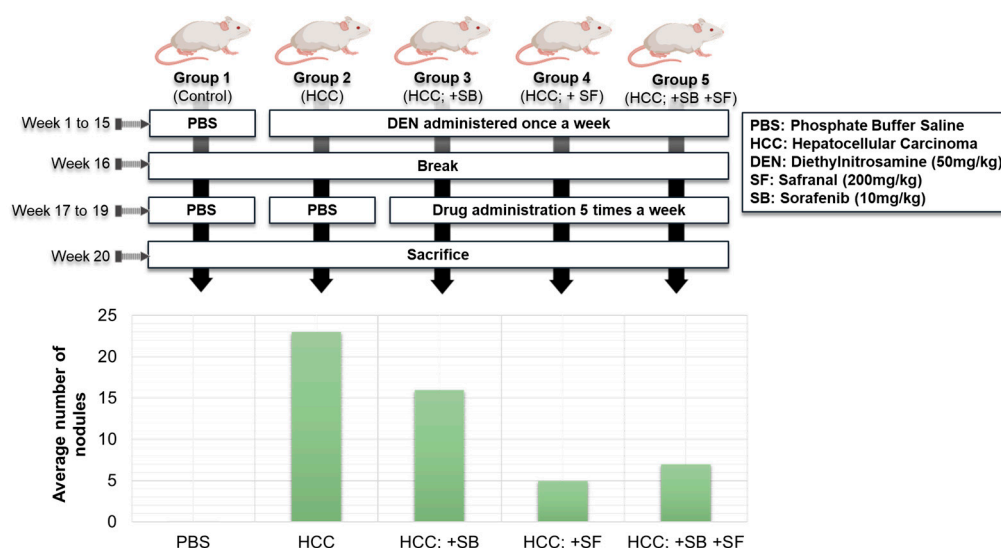


Figure 6. Experimental protocol and some results regarding safranal's action on tumor nodule proliferation given by granted patent US10568873B1. Adapted from Amin et al., 2020 [88] (Copyright-free figure).

Treatments with safranal (HCC + safranal) and safranal combined with sorafenib (HCC + safranal + sorafenib) reduced lesions compared to untreated animals. Safranal also significantly decreased lesions compared to treatment with sorafenib alone (HCC + sorafenib). Other results founded on the patent document show that safranal inhibits the proliferation of induced hepatic neoplasia and that it significantly increases the expression of the pro-apoptotic protein and significantly decreases the expression of the anti-apoptotic protein compared to the control groups, which confirms the apoptotic effect of safranal in liver tumors in rats [88].

One year later, Amin and Awad claimed a method and a therapeutic composition for treating liver tumors [89]. The method is applicable to various liver tumors, including hepatocellular carcinoma. In this method, a patient receives a first amount of sorafenib, followed by a second amount of crocin or its prodrug, with a weight ratio between 50:1 and 5:1. Crocin is administered first to sensitize tumor cells before exposure to sorafenib. The prodrug options include crocin, hemiacetals, hydrates, acetals, thioacetals, tautomers, silyl ethers, isomers, or combinations thereof. The detailed patent descriptions present experiments that were conducted to explore the therapeutic potential of crocin against HCC in male rats. The HCC was chemically induced in rats using DEN. Several biochemical, histological, and molecular marker analyses were conducted [89]. Figure 7 summarizes the rat experiments and gives the results of evaluations of the average numbers of tumor nodules observed in liver tissues.

The study results revealed significant therapeutic benefits when crocin was administered alone (60% of nodules reduction compared to the untreated group) and in combination therapy with sorafenib (74% of nodules reduction compared to the untreated group), whereas sorafenib when used alone reduced the number of nodules by only 30%. This highlights the synergistic anti-tumor effects of crocin and sorafenib in HCC in laboratory rats. While the exact mechanisms are not conclusively determined, the inventors hypothesized that crocin treatment triggers the activation of the intrinsic apoptotic pathway in liver tumor cells [89].

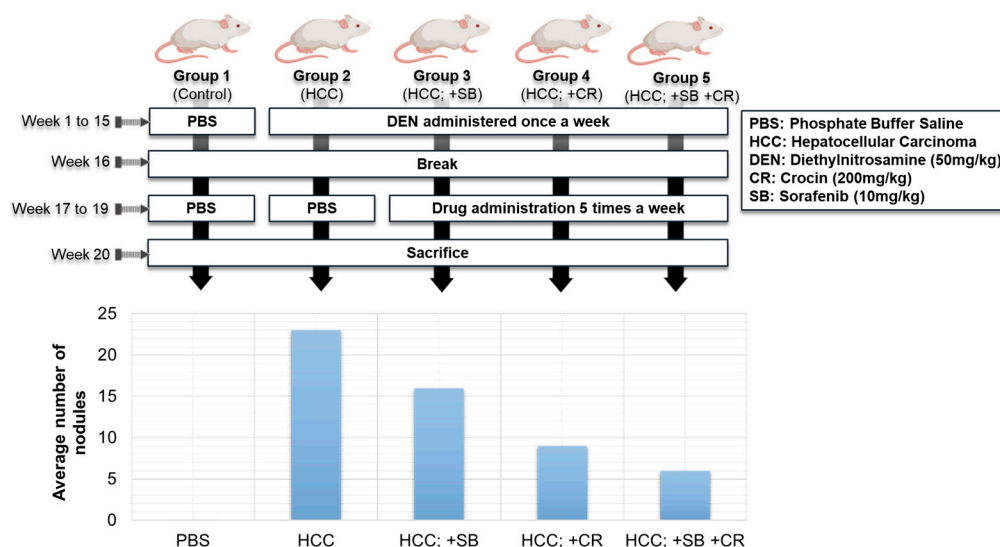


Figure 7. Experimental protocol and some results regarding crocin's action on tumor nodule proliferation given by granted patent US10933076B2. Adapted from Amin and Awad, 2021 [89] (Copyright-free figure).

4.3. Observations

In summary, these innovations not only help advance tumor treatment using saffron-derived components but also present a comprehensive approach to improving health through targeted compositions and formulations. This trend is set to grow even more in the near future. Indeed, several recent patent applications provide solutions to overcome the problem of the low water solubility of certain active compounds in saffron, especially crocetin, which is also unstable and poorly absorbed orally, considerably limiting its pharmacological efficacy [90]. This is particularly the case for applications that highlight the use of a more stable trans-crocetin form, proposing changes in the implementation of synthetic pathways that facilitate industrial production of the final product and limit its cost [91–94]. Trans-crocetinate has been the subject of a clinical trial investigating its safety and efficacy in newly diagnosed subjects who have undergone a glioblastoma biopsy. The results of the running-in phase, published in 2021, did not show any adverse safety signals. However, a large-scale randomized trial has not yet been conducted. Regarding crocin, a recently granted U.S. patent identifies it as an autophagy modulator and proposes its use for the treatment of tumors [95]. Indeed, autophagy is a process that intervenes in the regeneration of cellular components and whose dysregulation is associated with certain pathologies, such as tumors. For this reason, modulation of autophagy, which can be both cytoprotective and cytotoxic, is a promising therapeutic approach in tumor therapy [96]. In a clinical study begun in 2021, the corcin displayed an effect on cardiovascular dysfunction caused by breast tumor treatment. This was a randomized, double-blind, placebo-controlled, single-center clinical study.

5. Future Trends and Implications

Various studies indicate a promising future for saffron and its derivatives in clinical applications, with plans for expanded clinical trials across various therapeutic areas. In the next few years, trials will explore saffron's potential in cancer therapy, diabetes management, mental health conditions, and the stress response. These studies aim to further investigate saffron's efficacy and elucidate its underlying mechanisms in different disease contexts.

More recently, the randomized and double-blind placebo-controlled trial NCT04749576 is evaluating saffron supplements as an anti-inflammatory agent in patients with inflammatory bowel disease (IBD), specifically ulcerative colitis. The trial aims to assess if saffron can reduce inflammation and the need for immunosuppressants in 100 IBD patients. It

is investigating two different dosages of saffron compared to placebo, with a completion date of December 2023. This trial is directly testing the therapeutic potential of saffron in managing IBD [97].

Moreover, future trials will focus on saffron's effects on reproductive health, such as hormonal regulation, signaling pathways, and inflammatory processes. These studies could validate saffron's role in conditions like erectile dysfunction, dysmenorrhea, premenstrual syndrome, and libido enhancement [98]. Additionally, research will explore saffron as an adjunct to novel cardiovascular medications, leveraging its potential to mitigate cardiovascular risk factors to improve the cost effectiveness of these therapies and reduce morbidity and mortality.

Although saffron has been used traditionally for centuries, its widespread modern use warrants further evaluation of its safety profile in humans. The search results indicate that clinical trials assessing saffron and its major compounds, like crocin, have generally found them to be well tolerated at the studied doses. However, as with any substance, the potential for adverse reactions or idiosyncratic effects cannot be completely ruled out, especially with long-term or high-dose consumption. As saffron gains more popularity as a dietary supplement and functional food, continued pharmacovigilance and reporting of any adverse events will be crucial to fully characterizing its safety in diverse populations [99,100].

Overall, the future looks promising for the clinical applications of saffron and its derivatives, with a focus on expanding research efforts, optimizing dosages, evaluating safety, and exploring combination therapies across various therapeutic areas.

6. Conclusions and Outlook

Saffron and its key compounds have been extensively studied to determine their activities. We reported some of these studies, focusing on the antioxidant, anti-inflammatory, and anti-tumor actions of saffron. Thus, we documented these interesting effects and showed that, with standard doses, saffron and these extracts were non-toxic. While the provided search results cover various aspects of saffron's potential therapeutic effects and toxicity studies, there is limited information specifically addressing its safety profile and potential adverse reactions in humans with increased usage.

In the second part, we explored the current state of the use of saffron and its major compounds for tumor prevention and treatment, drawing insights from relevant patent documents. We established that patent activity in this field began in the mid-1990s, with significant innovations often rooted in traditional Chinese medicine, which leverages natural therapeutic formulations to enhance the body's defenses and target tumor cells. Many patents utilize the known anti-tumor properties of saffron compounds, indicating a rich integration of traditional knowledge and modern innovation. The observed increase in patent applications suggests that future advancements in this area are likely. Our analysis focused on granted patents that were published at various stages of the patent lifecycle depending on jurisdictional policies. Most patent authorities publish applications 18 months after the priority or filing date, regardless of grant status, while some only publish granted patents, keeping pending applications undisclosed unless granted. China leads in saffron-related patenting, with approximately 60% of the patents in our study originating there. We identified 271 patent applications and 25 granted patents, with only six granted patents relevant to traditional Chinese pharmacopeia. The apparent cessation of patent publications after 2012 is attributed to the matching score utilized in Elasticsearch. For a thorough understanding of the developments in saffron-related anti-tumor patents, a future study focusing exclusively on patent analysis would be beneficial. This approach would provide a more detailed and coherent examination of the patent landscape without overwhelming the reader with excessive detail in the current study.

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