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Case study

Model implementation of the legal regulation on medicinal plant cultivation for pharmaceutical purposes. Case study of *Crocus sativus* cultivation in Ukraine

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Abstract

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Crocus sativus L. (Iridaceae) is the source of saffron, a traditional spice and herbal medicine, usually cultivated in Southwest Asia and the Mediterranean. Saffron is a new niche food and medicinal plant in Ukraine. An important area of production, namely the application of Good Agricultural and Collection Practice (GACP) principles for obtaining high-quality saffron raw materials for the pharmaceutical industry, has been evaluated. The study was conducted on a plantation in Lyubimovka village, Kherson Region in Ukraine, from 2016 to 2021. The research object was *Crocus sativus* and the quality management system in the cultivation and harvesting of medicinal plants. The Ukrainian legislation on herbal drug production introduced guidelines by the World Health Organization (WHO) 'Good Agricultural and Collection Practice (GACP) for Starting Materials of Herbal Origin' in 2012. The Guidelines are recommendatory and not mandatory. However, these principles ensure that appropriate quality herbal raw materials are obtained. Implementing GACP principles with the example of saffron includes a description of the plant, sowing material, primary processing, sowing conditions, transportation and storage, packaging, quality control, and documentation. The presented results reflect the entire production process and show the prospects for obtaining high-quality raw materials. The study suggests the results of implementing the WHO GACP guidelines to guarantee the traceability of herbal raw materials and their reliable quality.

Keywords: *Crocus sativus*, cultivation, GACP, herbal raw material.

INTRODUCTION

The safety and quality of herbal medicines are a priority for health authorities and society. The pharmaceutical industry is one of the most demanding globally in terms of compliance. The production of herbal medicines is one of the specific areas, which is inextricably linked to those standards. Therefore, it is necessary to follow good practices, including adherence to operating procedures and critical points

throughout the technological process, ensure patient safety at all stages of drug development. This provides a high-quality, safe, reliable and effective herbal medical product commitment to good manufacturing practice (GMP), good laboratory practice (GLP), good clinical practice (GCP), and good distribution practice (GDP) is mandatory and controlled. Today, compliance with good agricultural practices (GAP) to ensure quality medicinal plant raw materials is only a recommendation.

The World Health Organization has developed guidelines for Good Agricultural and Collection Practice (GACP) (Collection Practices, 2003; Association, 2010), which is one of the practices in shaping the quality assurance system of pharmaceutical production (Medicines Agency, 2011). Compliance with these requirements guarantees the quality and safety of herbal medicines, which directly affects the safety and effectiveness of herbal medicines (Manufacturing Practice, 2007). The main objective of this proper quality assurance system for raw materials is to create growth and primary processing conditions that provide consistent and reproducible 'plant source materials' of the appropriate standard. The European Medicines Agency (EMEA) Committee (Medicines Agency, 2006a) has extended requirements specifically for the cultivation and processing of medicinal and aromatic plants (Association, 2010, 2016) in the European Union (Fig. 1). The production of medicinal and aromatic plants (MAP) requires a higher quality of raw material purity. Therefore, European Herb Growers Association (EUROPAN) (Association, 2016) proposed supplementing GACP. To support this approach, a 'Practical Implementation Guide' has been developed in the form of basic standard operating procedures (SOPs) on important GACP topics, accompanied by practical examples. EUROPAN offers guidelines for selecting growing conditions for medicinal plants, considering quality control. However, growing conditions can or should be adjusted depending on the situation on-site. These guidelines apply to the production of all plant materials that are used directly or in processed form for humans and (or) animals. They also apply to all production methods, including organic production by European standards.

Ukraine has favourable environmental conditions for plant cultivation and high-quality herbal raw materials (Shanaida et al., 2018). Pharmaceutical enterprises of Ukraine use cultivated and wild medicinal plants and imported plant raw materials. The production of herbal material from medicinal plants is characterised by the complexity of the technological process, which involves the stages of collection, sorting, drying, grinding, processing and storage. Compliance with these requirements guarantees obtaining quality raw material for production. The content of bioactive compounds in various plant organs is not constant. It depends on the conditions of the cultivation place, time of day, weather conditions, and some other, no less important factors (Quispe et al., 2021). The development of plant

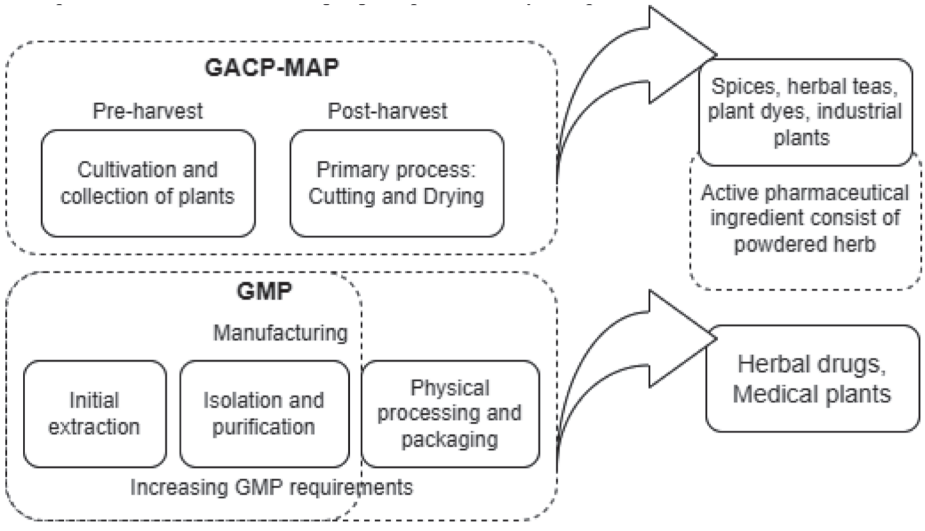

Fig. 1. General presentation of the relationship between the principles of plant cultivation (GACP) of medicinal and aromatic plants (MAP) and other manufacturing processes (GMP) in the production of herbal drugs for the pharmaceutical industry (after Medicines Agency, 2006a)

cultivation stages by GACP principles, considering local factors, will obtain raw materials with a given content of bioactive compounds.

Crocus sativus L. cultivation was started in Kherson Region (Ukraine) in 2015. Crop cultivation has covered almost all country regions (Mykhailenko et al., 2020). The plant is grown in Spain, India, Iran, Turkey, Greece, Italy and elsewhere (Fernández et al., 2010). Yields and quality of saffron are influenced by cultivation methods, processing and environmental conditions (Busconi et al., 2018; Maleki et al., 2017). Modern pharmacological studies indicate a high therapeutic potential of *Crocus* stigmas as a cytotoxic, antihypertensive, neuroprotective or ophthalmic agent (Xing et al., 2021). As a homoeopathic and (or) medicinal raw material, saffron is featured in the world's leading pharmacopoeias (Homoeopathic Pharmacopoeia, 2003; Medicinal Plants, 2007; Pharmacopoeia, 2014). Furthermore, since 2021, the State Pharmacopoeia of Ukraine has included a monograph about *Crocus sativus* stigmas (Pharmacopoeia, 2021).

The wide range of pharmacological action is due to the content of saffron chemical components, namely the apocarotenoids (crocins), the monoterpenoids safranal and picrocrocin, and phenolic compounds, amino acids, carboxylic acids, micro- and macroelements (Mykhailenko et al., 2019; Allen & Hatfield, 2004). Accordingly, the content of these components will affect the outcome of the pharmacological action. The development of standard operating procedures and adherence to the GACP on quality control of medicinal plants is necessary for the proper production of quality raw materials for the pharmaceutical industry (Manufacturing Practice, 1997).

The work aimed to analyse the current state of the regulatory system concerning the production of herbal raw materials in Ukraine and justify the feasibility of applying the GACP principles to the example of *Crocus sativus* (saffron) to improve the quality of the produced raw material. The study was conducted on the plantation of Lyubimovka village, Kherson Region, Ukraine, from 2016 to 2021. As a result, the Standard Operating Procedures (SOPs) for the cultivation of *Crocus sativus* were developed based on the analysis of guidelines and standards (Collection Practices, 2003; Medicines Agency, 2006a; Association, 2010, 2016; Standard, 2012) and numerous scientific publications.

LEGISLATION GOVERNING THE QUALITY OF RAW MATERIALS

Preparations to be supplied to the European market for medicinal products (active substance, intermediate or finished product) must comply with GMP standards (Standard, 2011). The manufacturer's main aim when applying GMP standards is to make sure that the product's safety, quality and efficiency are not violated and minimise the risk of loss to the business. The WHO GACP guidelines in the production process of herbal raw materials have been developed and implemented in the countries of the European Union, China, Japan, India, Malaysia and Ukraine.

The European Union regulates the production and release of traditional herbal medicines and the harmonisation of the European market herbal drugs by the Committee on Herbal Medicinal Products of the European Medicines Agency (Medicines Agency, 2021). The production of medicines in Ukraine is regulated by the Law of Ukraine 'On Medicines' (No. 123/96-VR of 04.04.1996). Previously, wild plant raw materials were collected according to the instructions 'Rules for collection and drying of medicinal plants: Collection of instructions' (Shreter, 1985) and 'Handbook of preparations of medicinal plants' (Ivashin, 1989). Since 2013, in Ukraine, the instruction 'Medicines. Good Agricultural and Collection Practice for Starting Materials of Herbal Origin. ST-N MOH 42-4.5: 2012' (the order of the Ministry of Health of Ukraine № 118 of 14.02.2013) (Table 1) has been adopted. These principles are quality assurance, highlighting the requirements of standardisation and quality indicators of herbal raw material. Requirements for establishing quality for raw materials are defined in the State Pharmacopoeia of Ukraine (Pharmacopoeia, 2021), in regulatory and technical documentation and international quality standards for each type of raw material. The GACP principles are recommended for the agricultural production of medicinal plants and their collection in nature. They consist of five sections: general introduction, good practice of cultivating medicinal plants, good practice of organising the collection of medicinal plants, and ethical and legal aspects.

The peculiarity of herbal preparations is the difficulty of standardising the starting materials of herbal origin. The GMP is based on the presence of the criterion 'reproducibility (identity)' of the composition

Table 1. Development of guidelines, recommendations and standards for good agricultural and collection practices globally and in Ukraine

Year	Guidelines, recommendations and standards
1998	EUROPAM issued the first draft of 'Good Agricultural Practice' (GAP)
1999	EMEA published comments on EUROPAM (EMEA/HMPWG/17/99 and 18/99)
2000	EUROPAM issued the first draft of 'Good Wild Craft Practice' (GWP)
2002	GAP and GWC were integrated into GACP
2002	EMEA published 'Points to consider on GACP for Starting Materials of Herbal Origin'
2003	WHO issued 'GACP for Medicinal Plants'
2006	EMEA and HMPC (Committee on Herbal Medicinal Products) issued 'Guidelines on Good Agricultural and Collection Practice (GACP) for Starting Materials of Herbal Origin' (2005)
2009	Ministry of Health of Ukraine issued guidelines ST-N MOH 42-4,0; 2011 'Drugs. Good Manufacturing Practice'
2010	EUROPAM 'Guidelines for Good Agricultural and Wild Collection Practices for Medicinal and Aromatic Plants' (GACP-MAP)
2013	Ministry of Health of Ukraine issued guidelines ST-N MOH 42-4,3; 2012 'Medicines. Good Practice of Cultivation and Harvesting of Raw Materials of Plant Origin'
2016	EUROPAM published guidelines 'A Practical Implementation Guide to Good Agricultural and Wild Collection Practices (GACP)
2020	Ministry of Health of Ukraine issued updated guidelines ST-N MOH 42-4.0; 2020 'Medicines. Good Manufacturing Practices'

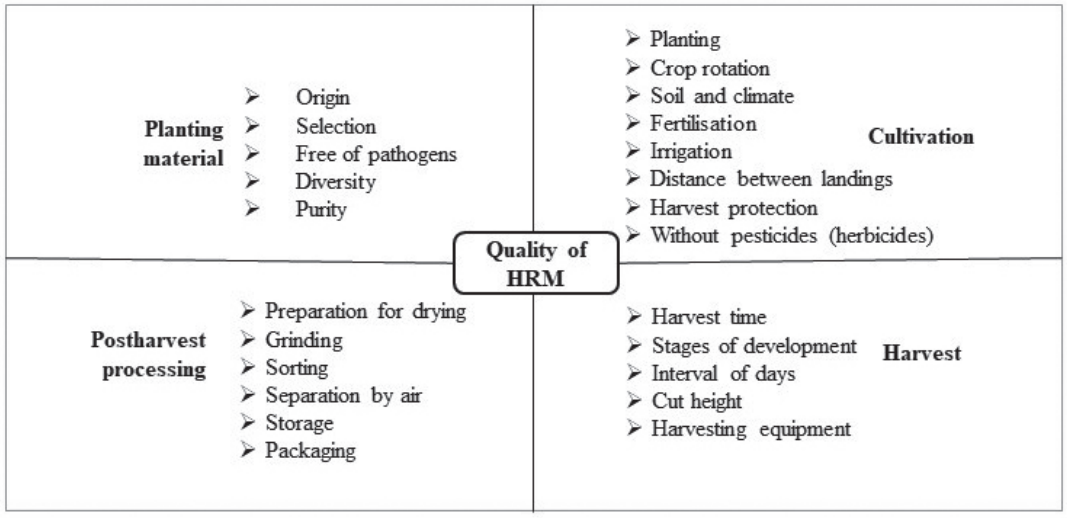

Fig. 2. Factors influencing the quality of herbal raw material

of the drug of each series (for plants – from harvest to harvest). The development of GACP standards for medicinal plants was based on the principles of GMP for an active pharmaceutical ingredient: mandatory standardisation of seeds or planting material, growing conditions with their documentation (indicating data on a specific place) cultivation, climatic features during the growing period, soil composition, irrigation, availability of fertilisers, etc.). Thus, each plantation must have its document, which records all the circumstances and factors during the growing period; date of harvest, method of drying plant material and packaging. In this way, it is always possible to trace the raw material from the field to the manufacturer of the phytopreparation, which guarantees the quality of the herbal raw material. The main factors influencing the quality of the original raw material and the content of bioactive compounds are shown in Fig. 2. The GACP guidelines should be considered in conjunction with existing documents and publications (Traditional Medicine, 2000, 2002; Manufacturing Practice, 2007; Working document, 2019; Quality Control, 1998; Medicines Agency, 2006b) on the quality assurance of herbal medicinal products and preservation (protection) of medicinal plants.

According to EU Directive 178/2002/EC, producers of foodstuffs and food additives and phytopreparations are obliged to ensure the traceability of the herbal raw material origin. According to the Food Agricultural Organization, Eastern European countries, including Ukraine, have significant prospects for developing medicinal crops, as evidenced by demand in domestic markets, positive trends in exports, and improving cultivation technologies and business (Report, 2017; Franic & Kleyman, 2012).

ETHNOPHARMACOLOGICAL AND MODERN CLINICAL APPLICATION OF SAFFRON

Saffron is the dried stigma of *Crocus sativus* and is the most expensive spice in the world (Mykhailenko et al., 2019). *C. sativus* has been cultivated for at least 3.500 years in Greece, Egypt and the Middle East. The name '*Crocus*' comes from the Greek word 'krokos' (saffron), which comes from the Semitic word 'karkom', one of the oldest names for this plant (Mohtashami et al., 2021).

The wild or original predecessor of the modern cultivated *C. sativus* was probably *Crocus cartwrightianus*, which, according to various opinions, originated either in Crete (in the Bronze Age) or in Iran (former Persia) (Nemati et al., 2019). However, Greece and Mesopotamia have been suggested as possible regions of origin for this plant. Some archaeological and historical research suggests that the domestication of saffron dates back to 2000–1500 BC.

Saffron was documented in the 7th century BC Assyrian botanical reference compiled by Ashurbanipal and has since been marketed and used for four millennia to treat several diseases. From its geographical origin, *C. sativus* slowly spread over most of Eurasia, later reaching parts of North Africa, North America, and Oceania. Now, saffron can be found in the Mediterranean countries and in the modern territories of Morocco, Iran, Kashmir, China and distant Australia (Fernández et al., 2010).

The first mentions of saffron are found in the history of Greece in 2300 BC. The use of saffron against various physiological conditions has been documented by all ancient Mediterranean, Persian and Arab cultures (Mousavi & Bathaie, 2011).

In traditional Chinese medicine, saffron is still used for menorrhagia, amenorrhea, melancholia, depression, shock, menstrual disorders, high-risk childbirth and postpartum lochiostasis (Xing et al., 2021). In India, Saffron is used for bronchitis, sore throat, headache, vomiting and fever (Leung, 1980). The Ayurvedic Pharmacopoeia of India ('Kumkum' is the Ayurvedic name for saffron) indicated the stigma and style in migraine, chronic sinusitis, and urinary obstruction and inflammation of the urinary tract (Experimental Cultivation, 1995). Additionally, saffron is used as an aphrodisiac, appetite stimulant, diaphoretic, contraceptive, antispasmodic and nerve soothing in India (Khare, 2007). It should be noted that there is mention of saffron for medicinal purposes or in food in almost every culture.

Even today, many studies focus on saffron, using modern analytical, pharmacological and clinical methods to validate its traditional use (Xing et al., 2021). Many publications are devoted to modern preclinical and clinical studies of the activity of saffron metabolites and its extracts (Bozorgi et al., 2021; Asadollahi et al., 2019; Mohtashami et al., 2021). The major constituents of saffron include essential oils (0.4–1.3%), picrocrocin, safranal and apocarotenoid glucosides known as crocins (Medicinal Plants, 2007; Jiang et al., 2018). Stigmas showed a pronounced antioxidant activity, inhibitory effect on blood coagulation (Hatziagapiou & Lambrou, 2018), and cytotoxic and antimutagenic activity (Bakshi et al., 2020). Iran (Akhondzadeh et al., 2010; Khalili & Hamzeh, 2010), China (Bian et al., 2020) and Japan (Zhang et al., 1994) are actively developing saffron preparations for the treatment of depression, epilepsy and mild Alzheimer's disease.

Saffron as a medicinal herbal raw material in Ukraine has been used relatively recently, with the beginning of plant cultivation in Kherson Region in 2016. However, the culture of stigma used in the folk medicine of Ukraine is not yet well developed. Most often, saffron is used to treat various stages of cancer, treat ophthalmic diseases and normalise blood pressure. However, officially published data was not found, only oral reports. Our research (Mykhailenko et al., 2021a) has shown cytotoxic (MDA-MB-231 and IGR39 cells line) and neuraminidase inhibitory activities of saffron from Ukraine.

Even though there are many studies on the cultivation methods and primary processing of *Crocus* stigmas (Busconi et al., 2018; Maleki et al., 2017),

the available data on saffron's chemical composition (Ghanbari et al., 2019) and the influence of environmental factors (Lage & Cantrell, 2009; Mykhailenko et al., 2021b; Mzabri et al., 2019) on the biosynthesis of metabolites for samples from different countries, we could not find published data or recommendations on the application of GACP principles for saffron cultivation. Earlier, we have presented the results (Mykhailenko et al., 2020) of an experiment on selecting optimal conditions for saffron cultivation in the climate conditions of Ukraine. Now, we attempted to explain the importance of implementing GACP principles to obtain high-quality herbal raw materials using the example of *Crocus* stigma.

IMPLEMENTATION OF GACP PRINCIPLES IN SAFFRON PRODUCTION

Standard operating procedures have been developed to implement GACP principles in *C. sativus* cultivation in Ukraine to obtain high-quality raw materials (saffron) (Mykhailenko et al., 2020). Among the provisions are general articles to ensure the quality of plant materials, such as 'Personnel and training', 'Buildings and premises', 'Equipment' and 'Documentation', 'Seeds and planting material', which must comply with GAP and GMP standards to ensure product quality. However, considering the climatic conditions of *C. sativus* cultivation in Ukraine, additional measures have been provided for the production and processing of herbal raw materials (stigmas), as compliance with these critical stages of production is necessary to ensure good saffron quality.

In previous works, with the assistance and advice of farmers from different regions of Ukraine, we have compared the conditions of saffron production, climatic characteristics of different areas of plant cultivation, soil composition, etc., on the chemical composition of *C. sativus*. As a result, we have formulated primary stages for proper *Crocus* cultivation by GACP principles in Ukraine. These stages reflect the requirements for environmentally sound cultivation technology, the rules of the harvest of *C. sativus* (stigmas), processing, and storage, which guarantee the high quality and safety of marketable products.

In September 2017, preliminary research was conducted on methods of saffron cultivation, yield determination and identification problems in the central saffron cultivation zone in Kherson Region, Kahovka district, with a temperate-continental, arid climate in the steppe south of Ukraine. The area of the plantation was 4 hectares. To develop and implement a plan for saffron cultivation in Ukraine following GACP principles in conjunction with the farm 'Saffron Lyubimovsky' on a flat, well-lit plantation, *C. sativus* corms 3–5 cm in diameter and weighing 15–30 g were planted. For planting, corms from the previous harvest of the farm were used. The planting took place in September. At the same time, the cultivation of Ukrainian saffron was carried out by the developed plan under GACP norms and had the same requirements for cultivation, which are observed by the leading producers: the same method of processing and storage.

STANDARD OPERATING PROCEDURE FOR THE PRODUCTION OF SAFFRON STIGMAS

Definition. Cultivated plant: *Crocus sativus* L., Saffron. Genus: *Crocus* L., Family: *Iridaceae* Juss.

Collected plant part. *Crocus* stigma (saffron) – three filamentous red stigmas (not including the yellow part), 25–30 mm long, exerting above the light purple petals of the flower (Fig. 3).

Plant description. A perennial herb (8–30 cm high) with an underground globular corm, with pale red-purple perianth of flowers, the flowering duration is 1–2 days. Stamens are slender, elongated and pale yellow in the middle of the tube, separated in the upper part by three dull, deep-red stigmas. The main constituents of saffron are picrocrocin, safranal, crocin, dimethylcrocetine and their aglycone crocetin, α- and β-pinene, 1,8-cienole, kaempferol glycoside derivatives (Medicinal Plants, 2007).

C. sativus cultivation technology according to traditional methods and the GACP guidelines consists of several stages: planting material selection, cultivation site selection, soil analysis, climate analysis, soil preparation, fertilisation, sowing, loosening and weeding, harvesting, drying and packaging. A detailed analysis of the peculiarities of saffron cultivation in Ukraine has been given by Mykhailenko et al. (2020).

Description of planting material. Dry, fleshy globular corms of spherical shape (Fig. 4), up to 3–5 cm in diameter, weighing 15–30 g, covered with

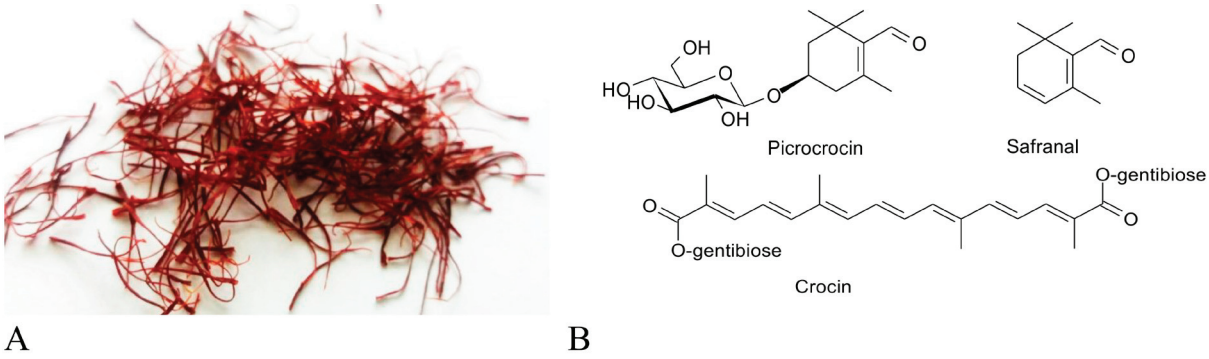

Fig. 3. Dried saffron stigma (A) and structural formulas of essential bioactive compounds (B)

Fig. 4. The field of 'Saffron Lyubimovsky' farm (A), planting material (*Crocus* corms) (B) and saffron flower (C) grown in Ukraine in compliance with the GACP principles. (Photos by O. Mykhailenko)

light brown scales, have roots.

Cultivation place. Growing should be carried out in an open flat area with good lighting. Productive cultivation of the plant in one place is possible for up to 5–8 years; then, it is necessary to carry out crop rotation.

Soil type. *Crocus* requires loose, well-drained soil to maintain the health of the corms due to the wet winter in Ukraine. In regions with low rainfall, good water holding capacity is essential. Saffron grows well in many soil types and textures, but it produces best in areas with sandy or loamy textures (Lage & Cantrell, 2009). The most optimal soil pH level should be from slightly acidic to neutral. Due to the change of seasonality in Ukraine, especially the southern regions are characterised by severe over-drying of the soil in late summer, with the absorption of carbonates up, due to which the upper soil layers become slightly alkaline, which should be considered before planting saffron, which prefers alkaline soils. Due to the use of the plants as medicinal raw materials, the soil should not contain heavy metals under the requirements of Pharmacopoeia (Homoeopathic Pharmacopoeia, 2003; Pharmacopoeia, 2009, 2014, 2021). Therefore, agrochemical analysis of the soil is mandatory. No heavy metals were found in the studied soil in *Crocus* growing area in Kherson Region (Soils, 1991).

Soil enrichment. Regular lime is applied on acid soils before ploughing, which allows for bringing the hydrolytic acidity to pH 5–8. To enrich the soil of the plantation, you can make organic fertilisers (humus)

(10 kg/m^2). Manure should be carefully composted before use; it must not contain human excrement. Mineral fertilisers, fumigants, or pesticides are not used in the cultivation of saffron.

***Fertiliser application*.** In the first years of the growing season after flowering and harvesting, at the beginning of leaf regrowth, it is possible to loosen between rows with simultaneous application of nitrogen fertilisers at a dose of 75–100 kg/ha. The depth of cultivation is 8–10 cm. At the end of the growing season, it is recommended to cultivate with the introduction of phosphorus-potassium fertilisers at a dose of 60–90 kg/ha of the active substance.

***Climatic conditions*.** Fluctuations in temperature and humidity have the most significant influence on the seasonal rhythm of saffron growth and development. At the end of August, when soil preparation begins for planting saffron corms, the average daily temperature in different regions of Ukraine is from 19 to 28 °C, while the difference with night temperature is 5–7 °C. At the end of August, the rainfall is still relatively low, 5–30 mm. Thus, the lack of excess moisture promotes good rooting of corms and is compensated by watering every 10–15 days. At the beginning of flowering (late September–early October), the average daily temperature drops to +10 °C, and rainfall is 30 mm. In addition, the duration of solar radiation in October is 173–175 hours. Therefore, saffron continues to bloom until late October – to early November. In November, the average daily temperature is from 0 to –5 °C, and the amount of precipitation is 27–35 mm. Thus, the conditions for harvesting are favourable. The best climatic conditions for high yields are precipitation in autumn, warm summers and mild winters (Mykhailenko et al., 2020).

***Sowing conditions*.** 7–10 tons/ha of dry corms, the planting depth is 15 cm, the distance between corms is 10 cm, and the distance between the rows is 15 cm (Fig. 4).

***Irrigation*.** Before the flowering period, soil watering is recommended for 10–12 days after planting. Exceptions: the presence of precipitation and groundwater, which makes the soil too moist. In Ukraine, the crop should receive about 800–1200 mm of water annually due to rainfall and (or) irrigation. Experimental experience shows that rain 10–15 days before flowering leads to good flowering and high productivity, while in drought conditions, you can expect small flowers with tiny stigmas.

***Weeds, pests, and diseases*.** Weed control uses herbicides in summer or autumn, before the start of the new *Crocus* season. In addition, good results are obtained by milling to a depth of 5 cm in summer after the death of the aboveground part. The risk of fungal diseases of corms can be minimised by treatment during rotational transplantation.

***Harvesting and yield*.** In Ukraine, *Crocus* blooms from early October to late November. Before the full bloom of flowers, the stigmas are collected by hand in the morning. Saffron yields range from 0.2 kg ha to 4 kg/ha worldwide. In Ukraine, the usual yields are 5–12 kg/ha.

Primary processing

***Drying*.** Dry whole (not crushed) stigmas in an electric dryer with a controlled temperature of 36–40 °C for 2 hours until the appearance of brittleness on the intense brown colour of the raw material.

***Storage*.** The product must be packed in airtight and light-protected containers or jars made of dark glass. The serial number must be signed, and it must be sent for qualitative analysis. It should be stored at 4°C.

***Quality control*.** For determining the saffron quality, the requirements of the food industry (ISO/TS 3632 standards (Standard, 2010, 2011)) and the pharmaceutical industry (Pharmacopoeia, 2021) describe the appearance of whole or crushed stigmas; morphological and anatomical description; investigate the loss in mass during drying and the mass fraction of volatile compounds; mass fraction of total ash; determination of the main metabolites of saffron stigmas – crocin, picrocrocin and safranal, which affect the colour; taste; aroma, respectively. Quality indicators differ according to the requirements (Table 1).

To conduct an external audit of the farm for compliance with the technological processes to the European requirements for the cultivation of the selected crop, audit protocols were developed and worked out. Technical regulations for the production of products were agreed upon and adapted to the growing conditions on the farm, which included the appropriate time limits for monitoring the cultivation processes, and the quality of the raw materials obtained, following the soil and climatic conditions of the economy.

Table 1. The main indicators for determining saffron quality by ISO 3632 (Standard, 2010, 2011) and the State Pharmacopoeia of Ukraine (Pharmacopoeia, 2021)

Indicator	Definitions and norms	
	Standard, 2010, 2011	Pharmacopoeia, 2021
Appearance	Dried, dark red, tangled, solitary or sitting on short columns of three stigmas with a serrated edge at the distal end	
Aroma	Characteristic, aromatic odour	
Taste	Spicy-bitter, slightly tart	
Length	No less than 2 cm	2–4 cm
Loss on drying	No more than 12%	No more than 12%
Total ash	No more than 8.0%	No more than 7.0%
Ash insoluble in 10% HCl	No more than 1.0% for categories I and II and not more than 1.5% for category III	No article
Identification	TLC and (or) HPLC: artificial dyes should be absent	TLC: detection of crocin and exclusion of falsification
Quantification	*Taste* (picrocrocin content λ_{max} 257 nm), $E^{1\%}_{1cm}$ max/min 70–30; *aroma* (safranl content λ_{max} 330 nm), $E^{1\%}_{1cm}$ max/min 50–20; *colour* (crocins content λ_{max} 440 nm), $E^{1\%}_{1cm}$ max/min 190–80	By the definition of specific absorption rate: for crocin – not less than $E^{1\%}_{1cm}$ 180, for safranal – not less than $E^{1\%}_{1cm}$ 30, for picrocrocin – not less than $E^{1\%}_{1cm}$ 60, in terms of dry raw materials

Raw materials of appropriate quality and specific volumes were obtained based on the work performed. Results of the research work 'Use of the principles of Good Agricultural and Collection Practice (GACP) for Starting Materials of Herbal Origin under cultivation of the *Crocus* (saffron) in Ukraine' were adopted for the implementation at the 'Saffron Lyubimovsky' farm (Kherson Region, Ukraine).

CONCLUSION AND FUTURE PERSPECTIVES

The presence of a large number of scientific works on the pharmacological potential of *Crocus* stigma and, at the same time, the high cost of the spice causing an increasing interest in the cultivation and production of the herbal raw materials – *Crocus* stigma (saffron). Various physical, chemical and geographic factors affect the quality of plant raw materials. Therefore, the need for the controlled cultivation of medicinal plants is constantly increasing. Of course, the WHO GACP guidelines should be considered a recommendation document, as they cannot serve as a comprehensive instruction to produce organic, environmentally friendly herbal medicines. But compliance with its provisions developed for a particular medicinal plant, considering climatic, geographical factors, features of the culture itself, and evaluating national, regional and international regulations, will ensure the production of quality and traceable plant raw materials. *C. sativus* is an essential medicinal and food plant that has been successfully cultivated in Ukraine. The stages of saffron cultivation are proposed by the GACP norms, which have been tested based on the 'Saffron Lyubimovsky' farm. Adherence to these principles in Ukraine, not only for saffron, but for all medicinal plants, will promote the development of medicinal plants and allow to form a raw material component for the production of natural, environmentally friendly and effective drugs for both domestic market and export. In addition, orderly agricultural production will ensure the rational use of wild stocks of medicinal plants and help prevent the circulation of low-quality medicinal plant raw materials in Ukraine.

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