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RESEARCH ARTICLE

Advances in Aqueous Extraction of Saffron Compounds to Enhance Stability and Bioavailability for Nutraceutical Applications

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Abstract

Saffron (*Crocus sativus* L.) is a highly valued spice and medicinal plant renowned for its bioactive compounds, crocin, crocetin, picrocrocin, and safranal, which confer potent antioxidant, anti-inflammatory, neuroprotective, and anticancer activities. However, their low stability, poor aqueous solubility, and limited bioavailability constrain their incorporation into nutraceutical formulations. Traditional extraction methods, often reliant on organic solvents and high temperatures, can degrade thermolabile components and pose environmental concerns. Recent advances in aqueous extraction technologies, including ultrasound-assisted, microwave-assisted, enzyme-assisted, subcritical water, and cold plasma-assisted methods, have emerged as sustainable alternatives that preserve structural integrity while enhancing extraction efficiency. These innovative approaches not only reduce solvent toxicity but also improve the release, dispersion, and functional retention of saffron constituents. Furthermore, integrating green extraction with nanoencapsulation, biopolymer stabilization, and delivery systems such as liposomes or hydrogels has shown promise in enhancing bioaccessibility and controlled release of crocin and related carotenoids in gastrointestinal environments. This review critically discusses emerging trends in aqueous extraction, their mechanisms of action, optimization strategies, and comparative efficiencies. It also evaluates how these technologies enhance the stability and bioavailability of saffron compounds in nutraceutical applications. Future perspectives emphasize the need for process standardization, industrial scalability, and in vivo validation to bridge laboratory findings with commercial development of functional foods and supplements.

Keywords: Saffron, Aqueous Extraction, Bioavailability, Stability, Nutraceutical.

1. Introduction

Saffron (*Crocus sativus L.*) has been prized for centuries as both a culinary spice and a therapeutic herb and has featured prominently in traditional medicine for its reputed antimicrobial, antispasmodic, aphrodisiac, anti-inflammatory, and anticancer properties (Marrone et al., 2024). The health benefits ascribed to saffron in ancient practices, ranging from pain relief to mood enhancement, have spurred modern investigations into its bioactive constituents (Sharma et al., 2020). Chief among these constituents are the carotenoid apocarotenoids crocin and its derivatives, as well as picrocrocin and safranal. Crocins are water-soluble carotenoid glycosides responsible for saffron's vivid golden-yellow color, and they include trans-crocetin di-(β-D-gentiobiosyl) ester, also known as crocin-1, as the most abundant form. Picrocrocin, a bitter glycoside and degradation product of the carotenoid zeaxanthin, imparts the characteristic taste of saffron, while safranal, a volatile monoterpene aldehyde produced from picrocrocin during drying, is chiefly responsible for the spice's aroma (Shahi et al., 2016;

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Gómez et al., 2022). Notably, the dried saffron stigma is recognized as the richest edible source of these rare bioactive carotenoid derivatives. These unique compounds have been shown to exhibit numerous pharmacological activities that underpin saffron's traditional uses (Cerda-Bernad et al., 2022). Crocin is a potent antioxidant and free radical quencher with noted anti-tumor and anti-inflammatory effects, and it has demonstrated neuroprotective properties in various models (e.g., preventing oxidative damage in brain, eye, and kidney tissues). Safranal and crocetin (the aglycone form of crocin) contribute additional bioactivities, such as antidepressant and neuroprotective effects, and together the saffron compounds have been reported to help counteract degenerative eye diseases (e.g., age-related macular degeneration), mood disorders, neurodegenerative conditions, metabolic syndrome, and even malignancies. Considering these multifaceted health effects, saffron extracts and isolated crocin are increasingly considered for incorporation into modern nutraceutical formulations. For example, as supplements for vision health or mood support. However, despite these promising benefits, formulating saffron's bioactives into effective nutraceutical products presents significant challenges due to their instability and poor oral bioavailability. Saffron crocins are chemically unstable and prone to degradation: they gradually lose potency when exposed to light, heat, or acidic pH. Likewise, picrocrocin can break down (for instance, into safranal during storage) and the aroma compound safranal itself is volatile, which together lead to losses of bioactive content over time.

In parallel, these compounds have inherently low bioavailability in conventional oral formulations. Crocins are large, polar molecules that are not readily absorbed intact. After ingestion, they must be hydrolyzed in the intestine by enzymes or gut flora to release the aglycone crocetin, which is the form that crosses into circulation. As a result, a significant portion of ingested crocin is metabolized before it can exert systemic effects. Pharmacokinetic studies indicate that only a fraction of orally administered crocin is absorbed (with about 40% bioaccessibility in a simulated digestion), and nearly all the absorbed dose appears in plasma as crocetin rather than as crocin. Moreover, the bitter picrocrocin has limited bioactivity in vivo because it is poorly absorbed from the gut. These stability and absorption hurdles reduce saffron's efficacy when delivered via traditional extraction or powder formulations, motivating the search for improved extraction and delivery methods. In response, there is growing interest in aqueous extraction methods to enhance the stability and bioavailability of saffron's active compounds for nutraceutical applications. Because saffron is a high-value commodity, it is imperative to employ efficient yet gentle extraction techniques that maximize recovery of its valuable compounds. Water-based extraction meets this need and aligns with green chemistry principles, avoiding organic solvents while remaining safe for human consumption and environmentally friendly. Notably, saffron's polar crocins and picrocrocin are efficiently extracted into water, whereas the use of harsh organic solvents is unnecessary for these hydrophilic constituents. Researchers are exploring various aqueous extraction techniques, from simple infusion and decoction (tea-like preparations) to advanced methods such as ultrasound-assisted extraction, microwave-assisted extraction, and subcritical water extraction, to maximize yield and preserve the integrity of saffron bioactives. These techniques can produce high-strength saffron extracts without the thermal or chemical stresses often associated with conventional solvent extraction, thereby minimizing the degradation of sensitive compounds. Aqueous extracts can also be directly incorporated into functional food and beverage formulations or used as starting materials for encapsulation in biocompatible carriers, facilitating better delivery of the actives to the body. Indeed, studies have shown that saffron aqueous extracts enriched in crocin can remain stable over extended storage; one report noted that a lyophilized aqueous saffron extract retained its crocin content for more than 15 months under ambient conditions. By eliminating organic solvent residues, such extracts are more suitable for nutraceutical use and can improve consumer acceptability. Moreover, initial evidence suggests that presenting saffron compounds in an aqueous matrix or in an encapsulated form can enhance their bioavailability by protecting them from digestion and promoting their release at absorption sites.

Consequently, focusing on aqueous extraction approaches offers a compelling strategy to harness saffron's full nutraceutical potential, yielding extracts with enhanced stability of crocin and related constituents and producing formulations that may deliver higher bioactive payloads in vivo. This solvent-free, clean-label approach not only improves the technical performance of saffron ingredients but also aligns with consumer preferences for natural products. In line with these considerations, the following review provides a detailed overview of recent advances in the aqueous extraction of saffron compounds. It discusses how these innovations improve the stability and bioavailability of saffron's bioactive ingredients for nutraceutical applications (Figure 1).

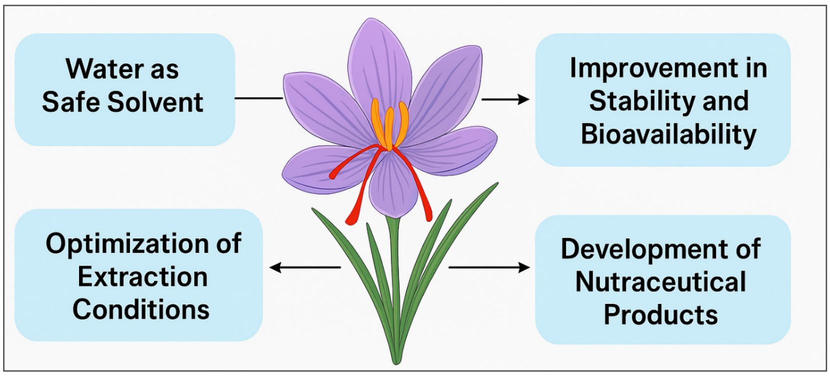

Figure 1. *Aqueous extraction and nutraceutical applications of saffron.*

2. Physicochemical Properties of Saffron

Saffron (*Crocus sativus* L.) possesses a uniquely complex physicochemical profile defined by its major bioactive constituents, including crocin, crocetin, picrocrocin, and safranal, which collectively determine its color, flavor, aroma, solubility behavior, and stability under processing conditions. The water-soluble carotenoid glycosides known as crocins are primarily responsible for saffron's intense yellow-orange coloration due to their extended polyene chain and multiple gentiobiose moieties, which enhance hydrophilicity and facilitate rapid dissolution in aqueous systems; their amphiphilic nature also allows limited interaction with lipid phases. In contrast, crocetin, the aglycone form, exhibits significantly lower solubility because the absence of sugar groups increases hydrophobicity, though its smaller molecular size improves membrane permeability and physiological uptake. Picrocrocin, a monoterpene glycoside, contributes to saffron's bittersweet taste and shows moderate stability in hydrated matrices but readily undergoes hydrolytic cleavage into safranal when exposed to heat, acidic conditions, or enzymatic reactions. Safranal, the primary volatile aroma compound, is highly lipophilic and exhibits significant volatility, thermal sensitivity, and susceptibility to oxidation, explaining the rapid loss of saffron aroma during prolonged storage, elevated temperatures, or UV exposure.

Collectively, these compounds endow saffron with complex optical properties, such as strong absorbance at 440 nm, which is widely used as a quality marker, and characteristic FTIR and fluorescence signatures linked to their conjugated structures. Physiochemically, saffron is hygroscopic and absorbs atmospheric moisture, altering its weight and potentially accelerating degradation reactions, particularly those involving glycosidic cleavage and lipid oxidation. Its color compounds are relatively stable at neutral pH but degrade rapidly in alkaline environments due to cleavage of the polyene backbone, whereas acidic conditions slow but do not fully prevent degradation. Thermal stability varies among constituents: crocins degrade at high temperatures but remain stable under moderate culinary heating, while safranal formation accelerates with temperature, contributing to aroma development but reducing picrocrocin content. Saffron's antioxidant capacity, driven mainly by crocins and crocetin, is strongly influenced by physicochemical factors such as pH, light, temperature, and oxygen exposure, all of which govern radical scavenging efficiency and storage lifespan. Additionally, particle size, grinding extent, and matrix interactions influence extraction efficiency, as finely ground saffron releases coloring matter more rapidly but is more prone to oxidative deterioration. The scanning electron microscopy (SEM) micrograph of saffron reveals a highly textured, porous surface with wrinkled folds and micro-voids, features that facilitate solvent penetration and enhance the release of crocins and safranal during extraction (Figure 2).

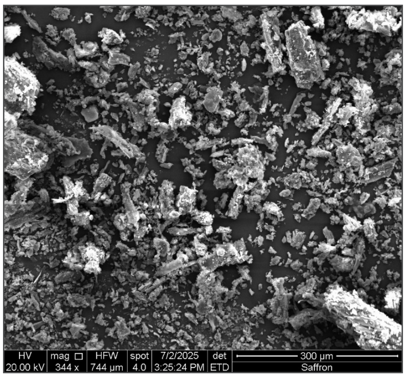

Figure 2. *SEM image of saffron, taken in the Microscopy and Imaging Center (Texas A&M University, College Station, TX, USA)*

Saffron's physicochemical qualities exhibit a delicate equilibrium of hydrophilic and hydrophobic components, whose stability and functioning are significantly influenced by processing and environmental conditions, necessitating meticulous management to maintain its purity and bioactive potential.

3. Aqueous Extraction Techniques for Saffron Compounds

3.1 Conventional Aqueous Extraction Methods (infusion and decoction)

Conventional aqueous extraction of saffron typically involves infusion (steeping) or decoction (simmering and boiling) of the saffron stigmas in water. Infusion entails soaking saffron in hot (not boiling) water for a short duration, allowing water-soluble compounds to leach out gently. This method is standard in culinary and traditional medicine uses of saffron, such as preparing saffron tea or pre-soaking threads in warm water before adding to recipes. Infusion is a gentle process that helps preserve volatile aroma compounds, such as safranal, by avoiding prolonged heating. In contrast, decoction involves boiling the saffron in water, often for a longer time, which can yield a more potent extract by extracting a larger fraction of soluble solids. However, the intense conditions of decoction risk degrading heat-sensitive constituents and evaporating volatiles. Saffron's aroma and some active compounds may be diminished by extended boiling; thus, infusion is generally preferred to retain delicate flavors and scents, whereas decoctions may maximize potency at the expense of some quality.

In aqueous extraction, water as a solvent will readily dissolve saffron's crocins (the glycosylated carotenoids responsible for color) and picrocrocin (the bitter principle), because these constituents are relatively polar. Indeed, the distinctive golden-yellow color of an infusion is due to crocin's high water solubility (conferred by its sugar moiety). By contrast, safranal, the volatile terpene aldehyde giving saffron its aroma, is hydrophobic and less efficiently extracted into water, especially without heat. Traditional practices of covering the container during infusion partly address this by trapping volatile oils. Still, purely water-based extraction is often incomplete, as saffron contains both polar and semi-polar compounds. Empirical studies confirm the limitations of water alone. For example, in one comparative extraction study, distilled water as the solvent yielded significantly lower levels of crocin, picrocrocin, and safranal from saffron compared to hydro-alcoholic mixtures under the same conditions. Water extracted only about half the crocin content achieved with 50% ethanol in that experiment, demonstrating that pure water can underperform because it cannot solubilize less-polar constituents. The use of a moderately polar solvent (e.g. 50% ethanol) was shown to achieve much higher yields of saffron's quality factors (with 50% ethanol > 50% methanol > water in efficiency). This indicates that while water alone extracts the primary glycosidic pigments, it may leave behind some apocarotenoids and volatiles that a mixed solvent could recover.

Optimization parameters for conventional aqueous extraction revolve around temperature, time, and saffron particle size. Mild heating (50–70 °C) can accelerate the diffusion of crocins into water. Still, excessive heat or prolonged exposure leads to degradation of those sensitive compounds (crocin decomposes with heat and light, losing color and bioactivity (Nazari & Asili, 2023). Traditionally, saffron threads are first crushed or ground to increase surface area, then infused in hot water (near boiling, ~90 °C) for 10–30 minutes. This timeframe balances extraction efficiency with compound stability. One standard quality test for saffron (ISO 3632) involves a controlled aqueous extraction and spectrophotometric reading of crocin, picrocrocin, and safranal at specific wavelengths, highlighting the practicality of water as a test solvent. Nonetheless, to maximize yield in purely aqueous extraction, long durations or repeated extractions may be used, but at the cost of potential hydrolysis or oxidation of crocin (notably, crocin's conjugated structure can break down, especially in acidic or very hot water).

Advantages of infusion/decoction methods include their simplicity and safety. They require no specialized equipment or hazardous chemicals, just water and heat, aligning with natural or traditional processing, desirable for nutraceutical applications. The extracts are directly consumable and free of organic solvent residues. Moreover, gentle infusions preserve more of saffron's aromatic profile, which could be important if the extract is intended for functional foods or supplements where flavor matters. Disadvantages, however, are notable as these methods can be time-consuming and inefficient. Yields of bioactives are relatively low unless large solvent volumes or multiple extraction cycles are used.

Even then, water might not effectively penetrate saffron's cellular structure without assistance, resulting in some compounds remaining unextracted. Decoction can marginally boost yield by softening and breaking down plant tissues, but as noted, it can also destroy or volatilize valuable constituents if not carefully controlled. Another problem is that traditional aqueous extraction methods are difficult to standardize, as slight variations in time or temperature can alter the phytochemical profile of the extract. In summary, conventional aqueous extraction of saffron via infusion or decoction is a baseline method that yields a pigment-rich, readily usable extract. It is environmentally friendly and suitable for home or small-scale preparation of nutraceutical infusions. However, due to incomplete extraction and potential compound degradation, these methods often underperform compared to more advanced techniques (Ali et al., 2022). This recognition has spurred research into improved green extraction technologies that can enhance the recovery of saffron's bioactives while maintaining water as the solvent. The sections below discuss several advanced aqueous-based extraction methods.

3.2 Ultrasound-Assisted Extraction (UAE)

Ultrasound-assisted extraction uses high-frequency sound waves (usually 20–40 kHz) to improve the extraction of bioactive compounds. The ultrasound waves create rapid compression and expansion cycles in the liquid, causing cavitation – the formation of tiny bubbles that violently collapse. These collapses generate localized high-shear forces and microjets of solvent that can break down plant cell walls and boost the movement of solutes into the solvent. In practical terms, applying ultrasound to a saffron-water mixture breaks open the stigmas more efficiently than static soaking, releasing crocin and other compounds into the water faster and more completely. UAE is considered a green extraction technique because it can achieve high yields with shorter extraction times and less solvent, often at lower temperatures than conventional methods.

For saffron compounds, the UAE has shown remarkable improvements in extraction efficiency. Recent studies have quantified these benefits, with Nissar et al. (2024) optimizing an ultrasound extraction of saffron stigmas using response surface methodology. By varying the methanol–water percentage, sonication time, and temperature, they found that moderate solvent polarity (~50% methanol in water), a short sonication time (~4–5 minutes), and an elevated temperature (~69 °C) maximized the yields of crocin, picrocrocin, and safranal. Under these optimized UAE conditions, the saffron extract's total phenolic content and antioxidant activity were significantly higher than those from conventional extraction (maceration). Specifically, the ultrasonically extracted sample showed 88% DPPH radical inhibition, compared with ~80% for the traditional extract, indicating greater recovery of antioxidant constituents. This demonstrates how ultrasound can boost both the yield and the quality of saffron extracts by releasing more bioactives without lengthy heating.

Another study highlighted that using ultrasound dramatically reduces the required extraction time. Traditional solvent extraction of saffron can take several hours to complete. In contrast, the UAE can often achieve yields like or better than those of conventional methods in just minutes. For instance, Slimani et al. (2024) reported that ultrasonic treatment with a probe-type sonicator of saffron floral waste in a sustainable solvent system could achieve optimal phenolic extraction in less than 45 minutes, whereas a comparable maceration might require overnight contact. Other reports recommend even shorter durations, with one analysis of phenolic extraction from Moroccan saffron by-products found that approximately 40 minutes of ultrasound was sufficient to obtain extracts with maximum antioxidant activity, beyond which no significant gains were observed. This indicates that prolonged ultrasonication yields diminishing returns, while a properly optimized short burst is ideal.

Mechanistically, UAE's effectiveness with saffron stems from both physical and chemical effects. The cavitational forces break apart saffron's cell matrix and increase the solvent penetration, so water or water-alcohol mixtures can contact internal pools of crocin and picrocrocin that were less accessible in simple soaking. Additionally, ultrasound agitation maintains the concentration gradient, and fresh solvent continually contacts the solid surface, thereby accelerating dissolution. The result is not only a higher yield but also potentially different extraction profiles, allowing the UAE to extract a broader spectrum of compounds. For saffron, some studies have noted that ultrasonication can help recover flavonol glycosides and phenolics from saffron petals or stamens in addition to the main apocarotenoids, enriching the extract's antioxidant repertoire.

Key parameters to optimize in the UAE include the ultrasonic power (intensity), frequency, extraction time, temperature, solid-to-liquid ratio, and any added cosolvents. Increasing ultrasonic power generally increases yield up to a point, but excessive power or long exposure could degrade sensitive molecules or cause local heating. Saffron's crocin, for example, while stable in aqueous conditions, could undergo cleavage if exposed to prolonged high-energy ultrasound and heat. Thus, many saffron UAE protocols use pulses or relatively short durations (5–30 min) to avoid compound breakdown. Temperature control is also essential, as ultrasound can heat the solvent through energy dissipation; maintaining a moderate temperature (often 40–60 °C) helps prevent significant thermal degradation of crocin, which is known to be heat-labile at high temperatures or prolonged exposure.

The advantages of the UAE for saffron are evident in the literature, including faster extraction, higher yield of target compounds, lower solvent requirements, and operation at milder conditions than decoction or Soxhlet extraction. Because the UAE can use water or water-based solvents effectively, it aligns well with producing food-grade saffron extracts for nutraceutical use. The ability to extract more crocin and picrocrocin means a more potent color and flavor extract, which can translate to smaller doses needed in a supplement or functional food. Additionally, by shortening the extraction time, UAE minimizes the window for oxidation of sensitive compounds. Disadvantages or challenges include the need for ultrasonic equipment and the scaling issues – large-scale ultrasonic extractors exist (e.g., ultrasound baths or industrial probe systems), but ensuring uniform cavitation on scale-up can be non-trivial. There is also a consideration of sonochemical effects, with ultrasounds that might promote free-radical formation in water that could, if unchecked, start to oxidize some constituents. To counter this, researchers sometimes conduct UAE under an inert atmosphere or add antioxidants when dealing with extremely sensitive extracts, though saffron's own compounds largely suffice as antioxidants.

In practice, UAE has been successfully applied to saffron stigmas and even saffron by-products. Masala et al. (2024) compared various green extraction methods for saffron floral waste and found that UAE outperformed conventional maceration in extracting polyphenols, yielding extracts with higher total flavonoid content and radical-scavenging activity. Combining UAE with other techniques can further enhance results, with one innovative approach using a hybrid of UAE and microwave-assisted extraction, applying ultrasound and microwave sequentially, which yielded an extract with exceptionally high phenolic content (31.56 mg GAE/g) and antioxidant power. This combined UAE–MAE extract contained abundant crocins (trans-crocin-4 and -3 as most abundant) and demonstrated superior ability to protect oils from oxidation. Such findings underscore how the UAE has become a cornerstone of advanced saffron extraction, making the process more efficient. It allows producers of saffron nutraceuticals to obtain high-strength aqueous extracts that would be difficult to achieve with simple infusion or maceration.

3.3 Microwave-Assisted Extraction (MAE)

Microwave-assisted extraction utilizes electromagnetic radiation in the microwave range (typically 2450 MHz) to heat the solvent and plant matrix rapidly from within. Polar molecules (like water) and ionic compounds absorb microwave energy and convert it to heat (dipole rotation and ionic conduction), causing a swift temperature rise. In plant materials containing moisture, this leads to internal steam generation, which can rupture cells, dramatically accelerating the release of phytochemicals into the surrounding solvent (Qi et al., 2020). For saffron, MAE is highly effective because saffron, when moistened with water, absorbs microwave energy efficiently. The internal moisture heats and helps to break the cell walls, freeing crocins, picrocrocin, and other compounds into the extraction medium in a matter of minutes.

Efficiency gains with MAE for saffron have been documented. Sarfarazi et al. (2020) evaluated MAE for extracting saffron's bioactive components and found it significantly boosted the yield of crocin, picrocrocin, and safranal relative to conventional solvent extraction. In that study, saffron samples subjected to microwaves yielded notably higher absorbance readings at the characteristic wavelengths (440 nm for crocin, 330 nm for safranal, 257 nm for picrocrocin) than those obtained by traditional maceration, indicating greater concentrations of each constituent. In fact, microwave treatment roughly halved the extraction time needed to recover a given number of saffron compounds, and in some cases, increased the yield by ~50% compared to conventional hot solvent extraction. For instance, when extracting crocin from gardenia (which contains crocin analogs), MAE produced 50% more yield than a usual hot soak, a result that aligns with similar principles in saffron extraction, highlighting the general power of microwaves to improve carotenoid extraction yields, a result echoed in saffron-specific research (Bachir-Bey et al., 2024).

Optimization parameters for MAE include microwave power, exposure time, solvent type and volume, temperature, and the moisture content of the plant. In saffron, using a small amount of water (or a water-ethanol mixture) as the solvent is common; sometimes the natural moisture in saffron (around 10–12%) is enough for the microwaves to interact without adding much extra solvent (Alvarez et al., 2021). Researchers often use intermittent microwave pulses to prevent local overheating, e.g., 30 seconds on, 30 seconds off, to keep the temperature within a desired range. The goal is to heat the matrix to the boiling point of the solvent (or slightly above under pressure) to rupture cells, then allow diffusion. Very short microwave bursts (on the order of 1–5 minutes total) have been successful for saffron. One study employing MAE found that essentially all measurable crocin could be extracted in under 3 minutes of microwave heating at 500 W, whereas a control extraction took 30–60 minutes of conventional heating to approach the same level (Karami et al., 2014).

The mechanism by which MAE enhances saffron compound recovery is two-fold: (1) Thermal effect, with rapid heating of the water inside saffron stigmas causes cell disruption and improved solubility/diffusion of compounds; (2) Non-thermal effects, with microwaves can orient dipolar molecules and possibly weaken bonds or interactions between target molecules and matrix (e.g. carotenoids bound to membrane proteins), making them easier to extract. In saffron, crocins may exist in cell vacuoles or bound to other cellular components; MAE can liberate these by essentially shattering the vacuoles. Observations under microscopy have shown that microwave-treated plant tissues often exhibit extensive cell wall breakage and fragmentation compared to gently heated ones. This means even the deeply embedded crocetin esters (crocins) in the stigma tissue are exposed to the solvent quickly.

Advantages of MAE for saffron extraction include great speed and high throughput potential. Many MAE protocols for botanicals can be completed in minutes, which is tremendously beneficial for processing large amounts of material efficiently (Boateng et al., 2023). It also tends to use less solvent, with sometimes just the moisture of the plant is enough, or a small volume of water, making it a greener approach. Because microwave heating is volumetric (heating occurs in the entire volume simultaneously), energy use is often more efficient than convective heating of a vessel. For saffron, which is a costly raw material, the ability to extract almost all valuable compounds in a short time means less material wasted and potentially lower production costs for saffron extract. Furthermore, MAE can be selective to some extent; by choosing appropriate conditions, one can favor the extraction of certain compounds. For example, a lower power/short duration microwave might preferentially extract more volatile or heat-sensitive fractions, whereas a longer/higher setting might pull out everything, including heavier phenolics. This tunability can be useful for tailoring saffron extracts to specific nutraceutical applications (e.g., focusing on crocin-rich extracts for color and antioxidant effects, or including more safranal for aroma and mood effects).

There are, however, disadvantages to MAE. Controlling the temperature is crucial as microwaves can create hot spots if the material or solvent is not uniform, potentially causing localized degradation of saffron compounds. Crocin's stability is limited to above ~80 °C, especially if exposure is prolonged. If a microwave extraction overshoots and boils the water excessively, crocin could hydrolyze or oxidize, leading to loss of color and efficacy. Therefore, modern MAE systems often have temperature feedback control. Another challenge is scaling up: while domestic or lab-scale microwave extractors are common, industrial continuous-flow microwave extractors require significant engineering (especially to ensure even microwave distribution in larger volumes). Also, MAE might not be suitable for very large batches if not designed properly, as the penetration depth of microwaves is limited (for water, around 1–2 cm at 2450 MHz), so material may need to be in a thin layer or moving through a waveguide for uniform treatment.

Nonetheless, MAE has been successfully demonstrated for saffron. In a comparative evaluation of green extraction methods on saffron floral by-products, MAE achieved high extraction efficiency with a low energy footprint. The process produced extracts rich in crocin and kaempferol derivatives in a fraction of the time required by conventional methods. Often, MAE is combined with other techniques (as noted, UAE and MAE hybrids, or MAE followed by enzymatic steps) to maximize yields. For example, Borras-Enriquez et al. (2021) found that combining ultrasonic pre-extraction with a microwave finish yielded an extract with a higher antioxidant activity (DPPH inhibition) than a simple maceration. This illustrates that MAE, especially in synergy with other methods, is a powerful tool to obtain potent aqueous saffron extracts rapidly. These advances in extraction help ensure that the full spectrum of saffron's bioactives can be harnessed for nutraceutical use without resorting to large volumes of organic solvents or lengthy processes.

3.4 Enzyme-Assisted Extraction (EAE)

Enzyme-assisted extraction involves adding specific hydrolytic enzymes to the plant material to break down cell walls and complex structures, thereby facilitating the release of bioactive compounds (Krakowska-Sieprawska et al., 2020). Plant cell walls are composed of cellulose, hemicellulose, pectin, and proteins, which can entrap target phytochemicals. In saffron, although the stigmas are relatively delicate, they still have structural polysaccharides that could hinder the full extraction of compounds (Holland et al., 2020; Maqbool et al., 2022). EAE uses enzymes such as cellulases, hemicellulases, pectinases, or proteases to hydrolyze these cell wall components (Stanek-Wandzel et al., 2024). By doing so, the physical barriers are removed or weakened, allowing water to penetrate more easily and dissolve compounds like crocin. Essentially, enzymes pre-digest the plant matrix under gentle conditions, usually 40–55 °C and pH adjusted to the enzyme's optimal level, which can greatly improve yields in a green and selective way (Vovk et al., 2023).

For saffron extraction, EAE has been explored particularly for saffron's floral by-products (petals and tepals), which contain phenolics and anthocyanins (Lotfi et al., 2015). These flower parts have sturdier tissues than the stigma and benefit from enzyme treatment. In one study on saffron petal anthocyanins, an enzymatic extraction using pectinase and cellulase greatly increased the yield of anthocyanin pigments compared to a control water extraction. The enzyme-treated samples released more color and antioxidants, indicating the enzymes effectively broke down the petal matrix that otherwise retained a portion of these compounds. Although the main nutraceutical interest of saffron lies in the stigmas (crocin), this approach is relevant when considering full valorization of the *Crocus sativus* plant. Even for stigma extraction, enzymes could help; for instance, cellulase might help rupture the dried stigmas further than grinding alone, and beta-glucosidase could potentially convert certain saffron precursors to active forms (though one must be careful, e.g., picrocrocin is a glycoside that yields safranal upon enzymatic cleavage).

Mechanistically, enzymes create porosities in the plant tissue: cellulases cut β-1,4-glucan chains in cellulose, pectinases break the pectic polysaccharides glue, and proteases can degrade structural proteins. In saffron stigma, which is the dried pollen-receptive part of the flower, these components are present in small amounts, but enough that enzymatic action can make a difference. As the cell wall and middle lamella are hydrolyzed, solvent access improves, and larger molecules can diffuse out. Crocin (which is a di-glycosylated crocetin) is a large molecule; improving the pore size via enzyme action can facilitate its leaching into water. Additionally, if enzyme specificity is targeted, one might release bound forms of compounds. For example, some phenolics might be bound to cell wall sugars and could be liberated by glycosidases. In fact, a study by Catinella et al. used a β-glucosidase enzyme on saffron corm wastes to generate safranal from picrocrocin, effectively increasing the yield of the volatile safranal (which in normal extraction mainly comes from dehydration of picrocrocin). This concept could be extended to nutraceutical extraction: enzymes might transform certain saffron components into more extractable or bioactive forms during the process.

Key parameters in EAE include enzyme type, enzyme concentration, incubation time, temperature, and pH. Saffron's valuable carotenoids and monoterpenes are sensitive, so EAE is typically done at mild conditions (around 50 °C or below) and for relatively short periods (1–3 hours), to avoid degradation of compounds like crocin (which starts degrading at prolonged heat or extremes of pH). The pH is often adjusted to ~4.5–5.5 when using pectinases/cellulases, as many of these work best in slightly acidic conditions. Fortunately, crocin is reasonably stable in that pH range for the duration of extraction. If proteases are used (less common for saffron, unless they try to break protein-carotenoid complexes), the pH might be different depending on the enzyme (e.g., neutral protease vs acidic). Another factor is solid-to-solvent ratio – with enzymes, you often make a thick slurry to maximize enzyme-substrate contact, then dilute or add more water after the enzymatic breakdown to extract the compounds. Agitation (gentle stirring) helps ensure the enzyme contacts all particles.

Advantages of enzyme-assisted extraction for saffron include its specificity and mildness. It's a very gentle method in terms of not requiring high temperatures or harsh chemicals: the catalysts are biological and operate under relatively benign conditions (often akin to food processing conditions). This helps preserve heat-labile saffron constituents. For example, one could do an enzyme treatment at 45 °C for a couple of hours and then immediately filter to get a crocin-rich extract without ever exposing it to boiling heat. EAE is also selective: by choosing enzymes, one might enrich the extract in certain compounds. For instance, using a β-glucosidase might increase free aglycones (like crocetin) by cleaving glycosides, whereas a general cellulase would simply maximize the release of all compounds. Since saffron's main compound crocin, is itself a glycoside, one must decide if keeping it intact is desired or not. Typically, we do want crocin intact (for color and known bioactivity), so most EAE protocols for saffron would avoid an enzyme that breaks it down, focusing instead on cell wall-degrading enzymes. The enzymes used are often food-grade (many pectinases or cellulases are used in juice processing), so the resulting extract can still be considered natural and safe for nutraceutical use.

Disadvantages of EAE include the cost of enzymes and potential contamination or downstream processing complexity. Enzymes are relatively expensive additives and may require inactivation or removal after extraction, commonly by heating to denature, which, if done, must be done carefully to not degrade saffron actives; or by filtration if enzymes are large. Also, enzyme extractions might leave residues (like oligosaccharides from partial breakdown) in the extract that could affect its clarity or stability. There's also an optimisation challenge; too little enzyme or time yields no benefit; too much could theoretically cause unwanted modifications, like if an enzyme accidentally cleaves a desired molecule. In practice, though, studies have shown significant benefits of EAE for similar botanicals: one report on enzyme-assisted extraction of polyphenols from saffron tepals found it improved total phenolic yield by ~30% compared to conventional extraction. The authors noted that enzyme treatment helped recover compounds that otherwise remained bound to the plant matrix. For saffron nutraceutical production, EAE could thus be a valuable step, perhaps in combination with other techniques (e.g., enzymes to pre-treat, then ultrasound to further extract – a combination that is logically very effective, using enzymes to open structures and ultrasound to expedite solvent flow).

In summary, enzyme-assisted extraction is a promising method to enhance aqueous extraction of saffron compounds, aligning with the principles of green chemistry. It operates under mild conditions that preserve compound stability, uses biodegradable biocatalysts, and can increase yields of crocin and related bioactives (Vardakas et al., 2021). While currently less common than UAE or MAE in saffron processing, EAE represents an area of advancement as producers seek to fully utilize saffron plant material (including traditionally discarded floral parts) and maximize the potency of their extracts. As enzyme costs come down and enzyme formulations become more tailored for specific plants, we can expect EAE to play a larger role in saffron nutraceutical extraction processes.

3.5 Subcritical Water Extraction (SWE)

Subcritical water extraction (SWE), also known as pressurized hot water extraction, uses water at high temperatures (typically 100–250 °C) under enough pressure to keep it in liquid form (above the saturation pressure) as a solvent. Under these conditions, water's physical properties change dramatically; its dielectric constant decreases with temperature, meaning the water becomes less polar and can dissolve compounds that normally would require an organic solvent. In essence, subcritical water at ~120–150 °C behaves somewhat like a mixture of water and ethanol or methanol in terms of solvent power (Masala et al., 2024). This makes SWE an attractive green technique to extract a wide polarity range of phytochemicals using only water, by tuning the temperature and pressure.

For saffron's bioactive compounds, SWE has shown the capability to extract both the highly polar crocins and moderately non-polar compounds like safranal efficiently. Sarfarazi et al. (2020) demonstrated that saffron's key constituents, crocin, picrocrocin, and safranal, can be extracted with subcritical water in short time frames (minutes) when appropriate temperature and time settings are used. In one such study, conditions of about 105–125 °C for 5–15 minutes under pressure yielded a robust saffron extract containing those target compounds (Hadizadeh et al., 2010). Using response surface methodology, the optimal point was found that maximized extraction efficiency while minimizing thermal degradation.

One study reported that pressurized liquid extraction of saffron with pure water or acidified water gave lower polyphenol yields and antioxidant activity than some other methods, possibly due to suboptimal parameter choices or partial degradation (Pappas et al., 2021). In their comparison, a combination of stirring and ultrasonication outperformed simple subcritical water, highlighting that each technique has nuances. It suggests that while SWE is powerful, it should be optimized (e.g., maybe adding a small percentage of ethanol to the water could further improve yields at a given temperature by moderating polarity, or choosing the right temperature). Despite these caveats, SWE remains a very appealing method for producing saffron extracts for nutraceuticals because it aligns with clean-label requirements and is scalable.

In summary, subcritical water extraction offers a way to tap into saffron's full phytochemical profile using only water as the medium, by leveraging high-temperature physics. It can extract crocins and even less polar compounds like safranal in one process. With careful control to avoid degradation, SWE yields potent extracts and can be integrated with downstream processes for concentration or purification. As the nutraceutical industry moves towards greener processes, techniques like SWE stand out as advanced methods to enhance the stability and bioavailability of saffron compounds (by obtaining a more complete extract) without conventional solvents.

To compare the efficacy, mechanisms, and practical implications of various aqueous extraction methods for saffron bioactives, Table 1 summarizes the major techniques discussed in Section 2. The next section discusses how these improved extracts are applied in various nutraceutical domains, and how their stability and absorption are further addressed in product formulations.

Table 1. *Summary of aqueous extraction techniques for saffron compounds.*

Technique	Principle	Key Advantages	Limitations	Relevant Outcomes
Conventional Aqueous Extraction	Soaking stigmas in hot water (infusion/decoction)	Simple, solvent-free, historically validated	Time-consuming, lower yield, compound degradation possible	Suitable for traditional preparations but suboptimal for crocin preservation
Ultrasound-Assisted Extraction (UAE)	Uses cavitation bubbles to disrupt cells and enhance diffusion	Fast, energy-efficient, increases crocin yield	Equipment cost, temperature rise may degrade compounds	Significantly higher extraction of crocin and phenolics vs. conventional methods
Microwave-Assisted Extraction (MAE)	Uses microwave energy to heat water inside plant cells	Rapid, high efficiency, selective for polar compounds	Risk of overheating, not suitable for all matrices	Efficient for extracting crocin with improved color strength
Enzyme-Assisted Extraction (EAE)	Hydrolytic enzymes break down cell walls and release bioactives	Enhanced release, mild conditions, effective for dried waste	Cost of enzymes, specificity required	Boosted extraction of crocin, picrocrocin, and phenolics from saffron and floral waste
Subcritical Water Extraction (SWE)	Uses high-temp pressurized water to extract polar to mid-polar compounds	Solvent-free, green, versatile compound solubilization	Requires pressure systems, high operational cost	Extracted crocin and safranal efficiently; good for large-scale, eco-friendly setups

4. Nutraceutical Applications of Aqueous Saffron Extracts

4.1 Cognitive and Mood Disorders

Saffron has been traditionally reputed to brighten the mood and enhance memory, and modern research is substantiating these effects for applications in cognitive and mood disorders (Kehtari et al., 2025). Aqueous saffron extracts, which contain the spectrum of saffron's active compounds (rocin, crocetin, picrocrocin, and safranal), have demonstrated antidepressant, anxiolytic, and neuroprotective properties in scientific studies. These findings have spurred the development of saffron-based nutraceuticals aimed at conditions like mild-to-moderate depression, anxiety, Alzheimer's disease, and age-related cognitive decline.

One of the most robust areas of evidence is depression and mood disorders. Multiple randomized controlled trials (RCTs) have shown that saffron extracts, commonly standardized to ~ 30 mg saffron/day, often taken as capsules of aqueous or hydroalcoholic extract, can alleviate symptoms of mild to moderate major depressive disorder. In fact, head-to-head trials have found saffron's efficacy comparable to standard antidepressant medications. For example, in a double-blind trial comparing saffron with fluoxetine (an SSRI) in mild-to-moderate depression, the saffron group experienced similar improvements in depressive symptoms as the fluoxetine group (Khaksarian et al., 2019). A meta-analysis of clinical trials concluded that saffron was as effective as SSRIs, like fluoxetine and citalopram, in improving depression scores, with no significant difference in outcome between saffron and pharmaceutical antidepressants (Stanciu et al., 2020). These results are remarkable for a natural extract and suggest that saffron's bioactive components modulate mood-related pathways. Mechanistically, saffron is thought to act on neurotransmitters: notably, its compounds inhibit the reuptake of serotonin in synapses, a mechanism akin to SSRIs (Chauhan et al., 2024). Consequently, serotonin levels in the brain increase, which correlates with improved mood and anxiolytic effects. Additionally, saffron may affect levels of dopamine and norepinephrine and modulate the HPA (hypothalamus-pituitary-adrenal) axis, contributing to an overall antidepressant effect (Shafiee et al., 2024).

Beyond clinical efficacy, saffron is also well-tolerated. Human trials report minimal side effects for saffron extract, often none beyond placebo. In a double-blind placebo-controlled study, 8 weeks of 30 mg/day saffron extract improved mood and emotional well-being in adults without causing notable adverse effects (no differences in hematological or biochemical profiles compared to placebo) (Ali et al., 2022). This safety profile is supported by toxicity reviews, which indicate that doses of up to approximately 1.5 g/day of saffron are considered safe in humans, with mild toxicity only observed at very high doses far exceeding those used therapeutically (Ayati et al., 2020). By comparison, synthetic antidepressants often have side effects like sexual dysfunction or drowsiness, with saffron's absence of these in studies is a potential advantage, especially for use in subclinical populations or those with mild symptoms.

Saffron's benefits extend to anxiety, stress, and even sleep. Some nutraceutical formulations of saffron (e.g., affron®, a standardized saffron extract) have been tested in people with stress and anxiety, with positive outcomes on mood and reduced anxiety levels. Preliminary evidence also suggests saffron can improve sleep quality. For instance, a trial in healthy older adults with sleep complaints found that a standardized saffron extract led to significant improvements in both subjective and objective sleep parameters compared to a placebo (Lang et al., 2025). The sedative and anxiolytic effects are likely related to the same neurotransmitter modulation and possibly interaction with GABAergic pathways, though research is ongoing. Importantly, these effects have been achieved using water-soluble saffron extracts that are rich in crocin, which is interesting because crocin itself has poor blood-brain barrier penetration until it is metabolized to crocetin. Crocetin is the deglycosylated form of crocin that can cross into the brain, and it's hypothesized that the cognitive effects of saffron are partly due to crocetin formed from crocin digestion. Crocetin and safranal are likely to work in tandem to produce neurochemical changes that enhance mood and cognition.

In the realm of cognitive disorders, particularly Alzheimer's disease (AD) and mild cognitive impairment (MCI), saffron has shown promise as a natural neuroprotective agent. A landmark clinical trial in patients with mild-to-moderate Alzheimer's disease found that 30 mg/day of saffron extract over 22 weeks significantly improved cognitive function, measured by the Alzheimer's Disease Assessment Scale–cognitive subscale, ADAS-cog, compared to placebo. Intriguingly, in that study saffron's effect was comparable to donepezil, which is a standard acetylcholinesterase inhibitor medication, in improving cognition, but with fewer side effects (Ayati et al., 2020). Patients on saffron showed improvements in their ability to remember and perform daily activities (activities of daily living), and there was no significant difference in efficacy between saffron and donepezil. Essentially, saffron worked as well as the drug over the 6 months. Moreover, saffron had an edge in tolerability: donepezil's known side effects (nausea, vomiting) were not issues with saffron. Results from four RCTs concluded that saffron significantly improves cognitive function in Alzheimer's and MCI compared to placebo and is not substantially different from approved Alzheimer's medications in its effects (Ayati et al., 2020). This has positioned saffron as a very interesting nutraceutical for brain health. The mechanisms behind saffron's neuroprotective and cognitive benefits are multifaceted. Saffron's crocin has been shown in preclinical studies to inhibit β-amyloid aggregation and deposition in the brain, a key pathology in Alzheimer's. It also has moderate acetylcholinesterase inhibitory activity (around 30% inhibition reported in vitro), meaning it can slow the breakdown of acetylcholine, a neurotransmitter important for memory (the same target as donepezil). Additionally, crocin and crocetin are powerful antioxidants and anti-inflammatory agents. They scavenge free radicals and reduce oxidative stress in neural tissues, which is beneficial because oxidative damage is implicated in neurodegenerative disorders. They also downregulate pro-inflammatory cytokines and pathways like NF-κB in the brain, potentially curbing neuroinflammation. For example, in a mouse model of neuroinflammation and trauma, saffron extract blocked the inflammatory cascade (including suppressing NLRP3 inflammasome activation) and improved outcomes. In human terms, this suggests saffron could help protect neurons from chronic inflammatory damage. Crocin has even been found to increase levels of brain-derived neurotrophic factor (BDNF) in some animal studies, supporting neuronal survival and plasticity.

Clinically, beyond Alzheimer's, saffron has been tested in MCI (mild cognitive impairment), which is often a precursor to dementia. One trial using saffron powder (125 mg daily) in MCI patients showed trends toward improved cognitive scores. However, results did not reach statistical significance, possibly due to the short duration or small sample size. Still, no adverse effects were observed, and given saffron's safety, it is being considered for longer-term studies in cognitive prevention. Its use in Parkinson's disease models has also been explored with positive neuroprotective results (e.g., crocin protecting dopaminergic neurons and improving motor function in toxin-induced Parkinsonian rats), hinting at broader neurological applications.

An essential aspect for nutraceutical formulation is bioavailability, with crocin, the main component in aqueous saffron extract, having low oral bioavailability as an intact molecule (it's hydrophilic and large). However, studies have found that after ingestion, crocin is primarily converted to crocetin (through gut enzymatic hydrolysis), which is absorbed and can be detected in circulation. Crocetin can cross the blood-brain barrier and is likely the active form reaching the brain (Wong et al., 2020). Some innovative formulations aim to improve crocin absorption (e.g., by encapsulating it or co-administering it with lipid to facilitate its conversion and uptake). Despite crocin's quirks, the clinical evidence clearly indicates enough active compounds are reaching target sites to have a therapeutic effect.

In summary, saffron aqueous extracts are emerging as effective nutraceutical options for the treatment of mood and cognitive disorders. They have demonstrated antidepressant efficacy on par with standard drugs in mild depression, anti-anxiety and sleep-improving effects in preliminary studies, and cognitive benefits in early Alzheimer's comparable to a leading medication but with better tolerability. The multifaceted pharmacology, from neurotransmitter modulation to antioxidant and anti-inflammatory action, underpins these benefits. For individuals seeking natural approaches to support mental well-being, memory, or complement conventional therapy, saffron supplements offer a compelling, evidence-based choice. Ongoing research is likely to clarify further optimal dosing, long-term effects, and whether saffron might also help in conditions like post-partum depression, obsessive-compulsive disorder, or age-related memory impairment (areas where initial studies are encouraging). So far, the convergence of traditional usage and scientific validation makes saffron a standout food-as-medicine for the mind.

4.2 Vision and Eye Health

One of the most exciting nutraceutical applications of saffron in recent years is in vision and eye health, particularly for age-related macular degeneration (AMD) and other retinal degenerative conditions (Bisti et al., 2014). Saffron's carotenoids (crocins and crocetin) and other constituents appear to have a protective effect on the retina – the light-sensing tissue at the back of the eye. Aqueous saffron extracts, rich in crocin, have been studied for their ability to improve visual function and protect against retinal damage.

Pioneering clinical studies in Italy about a decade ago first reported that saffron supplementation can improve visual outcomes in early AMD. In a landmark randomized trial, patients with early-stage age-related macular degeneration were given 20 mg of saffron extract daily for 3 months, compared with a placebo. The saffron group showed significant improvements in retinal flicker sensitivity (a measure of retinal function via electroretinogram) and visual acuity compared to baseline, whereas the placebo group did not. In practical terms, some patients could read an additional line on the eye chart after saffron therapy, an indication of improved visual sharpness. These short-term improvements were surprising because AMD is typically a slowly progressive disease with no expectation of spontaneous improvement. The results suggested that saffron was enhancing the function of damaged or vulnerable photoreceptor cells in the macula.

Encouraged by these results, the same patients were followed longer. A longitudinal follow-up study extended saffron supplementation to 15 months. It found that the visual benefits not only persisted but, in some cases, increased over the long term with continuous saffron use. Specifically, patients on sustained saffron (20 mg/day) maintained better macular function than their baseline and did better than expected for AMD progression. The authors reported that saffron supplementation improves macular function and maintains these improvements over long-term follow-up, suggesting a potential role in slowing disease progression. No significant adverse effects were noted, making saffron a safe long-term intervention (Falsini et al., 2010).

The presumed mechanisms by which saffron benefits the eyes are several-fold. Saffron's crocins are potent antioxidants and can absorb light; they are likely to help protect photoreceptors (rod and cone cells) from oxidative stress and light-induced damage. In rodent models, saffron supplementation protected the retina against intense light exposure that would generally cause photoreceptor death, preserving its structure and function. Saffron seems to upregulate protective stress-response genes in the retina. For instance, it has been shown to increase the expression of cytoprotective factors, such as heat shock proteins and anti-apoptotic genes, in retinal tissue, while downregulating inflammation-related genes.

4.3 Cardiometabolic and Antioxidant Effects

Saffron's bioactive compounds not only affect the brain and eyes but also have demonstrated benefits for cardiometabolic health, encompassing cardiovascular function, blood lipid profiles, blood glucose regulation, and systemic antioxidant status. Aqueous saffron extracts, which deliver crocin and related compounds, have been tested in both clinical trials and experimental models for their effects on risk factors associated with metabolic syndrome, diabetes, and heart disease. The findings indicate that saffron can play a supportive role as a nutraceutical in the management of these conditions.

Several studies have focused on saffron's impact on components of metabolic syndrome (MetS), including elevated blood sugar, dyslipidemia, hypertension, and a pro-inflammatory state. In a randomized clinical trial, 30 mg/day of crocin (a principal carotenoid from saffron) or an equivalent saffron stigma extract was given to patients with coronary artery disease, many of whom had underlying metabolic syndrome, for a period, and the expression of key metabolic and inflammatory genes was measured. The results were noteworthy, with crocin supplementation upregulating the expression of SIRT1 and AMPK in circulating blood cells, while downregulating LOX-1 and NF-κB expression. SIRT1 and AMPK are genes that promote antioxidant defenses and improve lipid/glucose metabolism (often called "metabolic master regulators"), whereas LOX-1 (lectin-like oxidized LDL receptor) and NF-κB are involved in endothelial dysfunction and inflammation. By increasing SIRT1/AMPK and decreasing LOX-1/NF-κB, saffron effectively shifted gene expression towards a cardioprotective, anti-atherosclerotic profile. SIRT1 and AMPK are genes that promote antioxidant defenses and improve lipid/glucose metabolism (often called "metabolic master regulators"), whereas LOX-1 (lectin-like oxidized LDL receptor) and NF-κB are involved in endothelial dysfunction and inflammation. By increasing SIRT1/AMPK and decreasing LOX-1/NF-κB, saffron effectively shifted gene expression towards a cardioprotective, anti-atherosclerotic profile. This gene modulation suggests that saffron can reduce inflammatory stress on blood vessels and enhance cellular pathways that improve metabolism and energy balance.

Clinical outcomes align with these molecular findings. A recent meta-analysis evaluated saffron's effects on glycemic control and cardiovascular risk factors in people with MetS or type 2 diabetes. The pooled data indicated that saffron supplementation led to significant improvements in fasting blood glucose and HbA1c (a marker of long-term blood sugar) as well as reductions in total cholesterol levels and blood pressure. For example, in one of the analyzed trials, after an 8-week course of saffron, patients saw a drop in fasting glucose by a few mmol/L and a small but significant decrease in HbA1c, suggesting better glycemic control, along with lower total cholesterol and systolic/diastolic blood pressure compared to controls. These effects, though modest, point toward saffron's beneficial influence on metabolic parameters. In terms of lipids, saffron and crocin have been observed to slightly raise HDL ("good") cholesterol and lower LDL ("bad") cholesterol or triglycerides in some studies, although results can vary by population and dose. Not all studies show large lipid changes, but an overall pattern of improved lipid profile and reduced atherogenic lipid peroxidation is reported.

One interesting study specifically looked at saffron's effect on the Pro-oxidant/Antioxidant Balance (PAB) in individuals with metabolic syndrome. PAB is a measure that integrates pro-oxidant load and antioxidant capacity in the blood. Crocin at 30 mg/day for 12 weeks was found to significantly reduce the PAB, meaning it tipped the scale towards a more antioxidant state in the body. This implies that saffron supplementation increased overall antioxidant capacity or reduced oxidative stress. Indeed, saffron is rich in carotenoids and phenolics that can neutralize free radicals. Crocin itself is a strong antioxidant, capable of quenching reactive oxygen species. In metabolic syndrome and diabetes, oxidative stress is a major contributor to endothelial dysfunction and insulin resistance. By ameliorating this, saffron could help improve vascular function and insulin sensitivity.

Markers of oxidative stress and inflammation, such as malondialdehyde (MDA, an indicator of lipid peroxidation) and C-reactive protein (CRP, an inflammatory marker), have also been tracked in saffron trials (Qin et al., 2025). Saffron supplementation tends to decrease MDA and CRP levels, reflecting reduced oxidative damage and inflammation. For instance, a subgroup analysis in one study showed MDA and CRP were significantly reduced in the saffron group compared to baseline, whereas isolated crocin in the same study also reduced these markers but had an even more pronounced effect on LDL and blood pressure. This highlights that whole saffron extract and its isolated constituent both confer antioxidant and anti-inflammatory benefits, sometimes with slightly different emphases; the whole extract might offer a broader range of antioxidants (flavonoids) that collectively lower oxidative stress, while crocin, as a single compound, strongly triggers certain protective pathways.

In cardiovascular health contexts, saffron has demonstrated protective effects on the heart and blood vessels (Rahim et al., 2025). In animal models of hyperlipidemia, saffron extract supplementation prevented increases in cholesterol and triglycerides and reduced atherosclerotic plaque formation. In hypertensive rats, saffron lowered blood pressure, likely due to its vasodilatory and antioxidative properties (some research suggests crocin can enhance nitric oxide production in endothelium, aiding vasodilation). Furthermore, saffron's crocetin has been observed to improve oxygen diffusion and utilization. It was studied for improving oxygenation, which could benefit tissues during ischemic episodes (Shah et al., 2021). In a human context, one trial found that adding saffron to the regimen of patients with stable coronary artery disease improved their antioxidant status and had favorable effects on their lipid profile. Another found that saffron (or crocin) supplementation in patients who had undergone angioplasty reduced inflammatory cytokine levels and improved endothelial function over time.

Saffron may also help with weight management and liver health indirectly by improving metabolic parameters. There is some evidence that saffron extract can reduce appetite and snacking. One study in overweight women found saffron intake led to the reduction of between-meal snacking and slight weight loss, possibly by influencing serotonin-related satiety signals (Gout et al., 2010). While weight loss effects are mild, any improvement in diet adherence can help metabolic syndrome patients. Regarding the liver, saffron's antioxidant effect has been shown to lower liver enzymes in people with fatty liver disease, hinting at less liver inflammation.

From a nutraceutical formulation perspective, aqueous saffron extracts high in crocin are convenient for cardiometabolic uses because crocin is water-soluble and can be incorporated into drinks or capsules easily. However, crocin's low bioavailability means high-dose extracts (30 mg of crocin corresponds to a few hundred milligrams of saffron extract) might be needed for pronounced effects. Some products combine saffron with other known cardiometabolic supplements (like cinnamon or chromium for glucose control, or bergamot for lipids) to create synergistic formulas. The advantage of saffron is that it addresses multiple facets: antioxidant, anti-inflammatory, and metabolic regulation, all in one.

It's worth noting that saffron has also been studied for its anti-diabetic properties in the context of pancreatic function. In diabetic animal models, saffron extract protected pancreatic beta-cells from oxidative destruction and improved insulin secretion. Crocin has been shown to upregulate PPAR-gamma (a nuclear receptor that improves insulin sensitivity) and reduce gluconeogenic enzyme expression in the liver, thereby lowering blood sugar (Fang & Gu, 2020). These mechanistic insights support clinical findings of better glycemic control with saffron supplementation.

In cardiovascular terms, saffron's anti-inflammatory action (like reducing NF-κB activity, as noted earlier) could help stabilize arterial plaques and prevent their progression or rupture, and its ability to lower LOX-1 expression means it could reduce the uptake of oxidized LDL by vascular wall cells, a key step in atherogenesis (Kamalipour & Akhondzadeh, 2011). After crocin administration in CAD patients, not only were gene markers improved, but patients also had trends toward improved cholesterol ratios and less oxidative modification of LDL. While these nutraceutical effects are supportive, they are valuable for overall risk reduction.

In summary, saffron extracts offer multiple cardiometabolic benefits as they modestly improve blood sugar control, aid in healthier lipid profiles, lower blood pressure by a few points, and strongly enhance antioxidant defenses while dampening inflammation (Sani et al., 2022). These effects can contribute to reduced risk of atherosclerosis, better management of diabetes or pre-diabetes, and improved vascular function. The use of saffron as a cardiometabolic nutraceutical is particularly appealing because of its safety and the fact that it tackles both metabolic and oxidative aspects of the syndrome. It aligns well with a holistic prevention strategy, combining diet, exercise, and supplements. People with metabolic syndrome or those who simply want to maintain heart health might take saffron extract alongside other interventions to capitalize on these protective effects. As research continues, we may better define optimal dosing (some studies suggest 100 mg/day saffron stigma powder or ~30 mg crocin as effective doses) and treatment durations. But even current evidence positions saffron as a valuable natural adjunct for cardiovascular wellness and metabolic balance, which could complement conventional therapies (e.g., using saffron plus diet changes to help lower a patient's cholesterol so that a lower dose of statin is needed, etc.). The broad antioxidant effect also means saffron could help reduce oxidative stress throughout the body, contributing to better outcomes in various chronic conditions where oxidative damage is a common thread.

4.4 Anti-cancer and Chemopreventive Uses

Saffron has a long history of being studied for its potential anticancer properties, and modern science has identified several mechanisms by which saffron compounds may exert chemopreventive and antitumor effects. Although saffron is not a mainstream cancer treatment, aqueous saffron extracts and isolated crocin have shown promising activity in cell-based and animal cancer models (Bhandari, 2015). They are being researched as complementary nutraceuticals that could help prevent or serve as adjuncts to conventional therapy. In vitro (cell culture) studies have demonstrated that saffron extract and its components can inhibit the growth of various human cancer cell lines (Geromichalos et al., 2014). These include cancers of the colon, breast, lung, prostate, pancreas, and others. The effects are often dose-dependent: as the concentration of saffron extract or crocin increases, cancer cell proliferation is suppressed and markers of apoptosis (programmed cell death) rise. For example, crocin has been shown to significantly reduce the viability of colorectal cancer cells by inducing apoptosis and cell cycle arrest (Bajbouj et al., 2012). In one study, crocin triggered DNA fragmentation and cell cycle arrest in a human pancreatic cancer cell line, which are hallmarks of apoptosis and an effective anti-cancer action (Bakshi et al., 2010). Similarly, saffron's ethanolic extract induced apoptosis in leukemia and sarcoma cells in culture and prevented their replication. The activity range is impressive, as saffron bioactives exhibit antiproliferative effects across various tumor types, suggesting a common mechanism, such as inducing oxidative stress in cancer cells, disrupting DNA synthesis, or affecting shared survival pathways.

One major mechanism identified is saffron's effect on cellular redox balance and mitochondrial function in cancer cells (Shakeri et al., 2020). Crocin and crocetin can produce reactive oxygen species within cancer cells to a level that triggers cell death, while normal cells, being less metabolically stressed, are less affected. Saffron also modulates gene expression in cancer cells by regulating pro-apoptotic genes, such as Bax and caspases, and downregulating anti-apoptotic and proliferation-related genes, such as Bcl-2 and cyclins (Mousavi et al., 2009). Additionally, saffron can inhibit telomerase activity in cancer cells, an enzyme that tumors often activate to become immortal. By blocking telomerase, saffron compounds may reduce the replicative capacity of cancer cells.

In vivo (animal) studies have provided further evidence of saffron's chemopreventive potential. In mouse cancer models, saffron extract administration has led to smaller tumors and slower tumor progression (Chermahini et al., 2017). For instance, in a murine model of colorectal cancer, saffron given in the diet reduced the number of precancerous lesions and tumor incidence. In studies of skin cancer, topical or oral saffron reduced tumor formation after exposure to carcinogens. Moreover, saffron appears to enhance the efficacy of specific chemotherapy agents when combined, while also protecting normal tissues from chemo's side effects (an exciting dual role). A study investigating immunotherapy for cancer found that adding saffron (crocin and safranal) improved outcomes: in vivo, mice treated with saffron had reduced tumor mass and increased body weight (as opposed to cancer cachexia-induced weight loss) compared with untreated controls. The saffron-treated mice also showed lower levels of certain immunosuppressive factors, implying saffron may bolster the immune system's ability to fight tumors (Feng et al., 2025).

When it comes to human clinical evidence, it is still in the early stages. Small trials have been conducted to test saffron or crocin in cancer patients, mainly to assess safety and any potential synergistic effects with standard treatments. One double-blind, placebo-controlled pilot trial in patients with advanced esophageal squamous cell carcinoma tested crocin (30 mg/day) during neoadjuvant chemoradiation (Javadinia et al., 2023). Unfortunately, the results did not show a significant difference in pathological complete response rates or survival between the crocin group and the placebo group. This suggests that, at least in that case, crocin did not clearly improve the effectiveness of standard therapy. However, it's important to recognize that such trials are difficult (often involving small sample sizes, late-stage disease, etc.), and a lack of significant benefit does not rule out more subtle or long-term advantages. On a positive note, crocin was well-tolerated in patients, with no additional toxicity to the intense chemoradiation regimen.

Chemoprevention, which involves using agents to prevent cancer in high-risk individuals, is another area where saffron is being considered. Because saffron is rich in antioxidants and can boost the body's antioxidant enzyme activities, such as glutathione-S-transferase in the liver, which detoxifies carcinogens, it could help neutralize cancer-causing free radicals or toxins. Saffron has also been shown to promote phase II detoxification enzymes in animal tissues, a classic cancer-preventive mechanism like how sulforaphane in broccoli works. For example, giving saffron to rodents exposed to a known carcinogen significantly lowered tumor incidence compared to the control group, suggesting a protective effect during the initiation phase of cancer development. By lowering inflammatory mediators (as discussed in the cardiometabolic section, saffron reduces NF-κB activity and CRP levels

Moreover, saffron's anti-inflammatory properties contribute to its chemopreventive effects, as chronic inflammation is a risk factor for many cancers. By lowering inflammatory mediators, saffron reduces NF-κB activity and CRP levels, creating a less pro-tumorigenic environment in the body (Zamani et al., 2022; Yu et al., 2024).

Another intriguing property is that saffron can *sensitize* cancer cells to chemotherapy or radiation. In lab studies, combining sub-lethal doses of saffron extract with low doses of certain chemo drugs resulted in greater cancer cell kill than either alone. This suggests saffron might impair cancer cells' defenses (for instance, by glutathione depletion or inhibiting efflux pumps), making them more vulnerable to conventional treatments. Clinically, this synergistic potential remains to be fully tested, but it's a promising concept: using a natural compound to both hit the cancer and protect normal cells (as saffron seems to do for the heart and kidneys in toxicity studies).

In terms of nutraceutical usage, no one is suggesting that saffron alone can cure cancer. Rather, saffron extract could be recommended as a complementary supplement. For example, for someone in remission wanting to reduce recurrence risk, or for someone undergoing therapy who is interested in integrative approaches, with oncologist approval. Its safety profile and general health benefits (mood lifting, appetite improvement) can also improve the quality of life for cancer patients. Interestingly, saffron's known effect of improving mood can be very relevant in cancer care, where depression is common.

One challenge is the dosing, as the amounts of saffron or crocin used in anti-cancer research are often higher than those for mood or eye health. For creating chemicals, they sometimes use the human equivalent of several hundred milligrams of saffron extract per day. For practical human use, if one were to take saffron supplements for cancer prevention, they might take 100 mg of extract daily, which is around 3 g of saffron spice equivalent, or more, as tolerated. Whether this is needed or if lower doses suffice remains unclear.

In summary, saffron exhibits a multi-targeted anti-cancer profile in preclinical models: it can induce apoptosis, stall cell division, inhibit tumor angiogenesis, modulate the immune response, and protect normal cells from damage. Its main bioactive, crocin, appears to be a key player, but safranal and crocetin also contribute to the anti-tumor effects. For instance, safranal has shown cytotoxicity in certain cancer cell lines, and crocetin can inhibit metastasis in models by affecting matrix metalloproteinases (Mishra & Mishra, 2023). While human clinical evidence is still emerging and somewhat mixed, with one trial showing no significant benefit in a specific setting, saffron remains an intriguing chemopreventive nutraceutical candidate. It can be combined with standard treatments without adding toxicity and may improve the tolerability of those treatments. Patients and healthcare providers are beginning to consider saffron in integrative oncology plans. For example, using it alongside vitamin D, curcumin, green tea extract, etc., as part of a comprehensive approach to prevent cancer or support conventional therapy. Ongoing research will clarify optimal strategies for using saffron against cancer, including which cancer types might benefit most and how to integrate it effectively. For now, saffron stands as a shining example of a spice with potential roles beyond flavor, possibly helping to fight one of humanity's toughest diseases.

4.5 Delivery Systems and Functional Food Formulations

Saffron's high-value bioactive compounds have spurred interest in developing effective delivery systems and functional food formulations to maximize its health benefits. Saffron has long been incorporated into a variety of foods, ranging from dairy products (milk, yogurt, and cheese) and desserts to pasta, baked goods, jams, and even beverages like herbal teas (Bagur et al., 2017). These uses capitalize on saffron's distinctive color, flavor, and antioxidant properties to enhance nutritional profiles and sensory appeal. However, the integration of saffron into foods is challenging because its key constituents are chemically sensitive. Crocin, the principal water-soluble carotenoid responsible for saffron's color, is highly prone to degradation once extracted from the stigma; exposure to adverse pH, elevated temperature, oxygen, or light can rapidly decompose this compound (Ardakani et al., 2024). Likewise, other saffron actives such as safranal (aroma) and picrocrocin (taste) are volatile or environmentally labile, leading to losses during processing and storage. Therefore, recent research has focused on protective delivery systems that maintain saffron's bioactive integrity and improve its stability in functional foods.

One major approach is microencapsulation, which involves entrapping saffron extracts or compounds within protective matrices. Microencapsulation shields saffron's sensitive components from degrading factors and allows their controlled release in the target food product. For example, spray-drying techniques have been employed to encapsulate saffron extracts using food-grade wall materials like maltodextrin, gum arabic, and gelatin. This method can significantly retain saffron's bioactive components during drying and storage. Rajabi et al. (2015) demonstrated that spray-drying saffron with such wall materials preserved the crocin content and antioxidant activity effectively. In another study, saffron (and even beetroot) extracts were co-encapsulated in matrices of maltodextrin, modified starch, gum arabic, and chitosan, which were then incorporated into a chewing gum formulation. This indicates the versatility of spray-dried saffron powders for use in functional confectionery while protecting the active pigments and flavors. Beyond spray-drying, hydrogel-based encapsulation has also shown promise. Saffron's bioactives have been encapsulated in calcium–alginate gel beads via extrusion methods, achieving remarkably high encapsulation efficiencies. In one case, over 99% of crocin was retained in alginate microcapsules (at initial loading) under optimized conditions. Such alginate encapsulation requires no high temperatures or organic solvents, thereby minimizing crocin's degradation, and yields smooth, spherical beads that can be incorporated into foods or supplements (Rahimi & Movahedipour, 2025). The alginate matrix not only prolongs saffron's shelf-life by shielding it from oxygen and light but also allows for controlled release of the core compounds during digestion or food consumption. Overall, microencapsulation techniques like spray-drying and hydrogel bead formation play a crucial role in formulating saffron-enriched foods by preserving sensitive constituents and improving their handling properties.

In parallel, emulsion-based and nano-delivery systems have been developed to further enhance the stability and bioavailability of saffron's bioactives. The use of multiple emulsions for nanoencapsulation of saffron extracts was notable, with a double-layered water-oil-water emulsion stabilized with biopolymers (pectin and whey protein concentrate) created to encapsulate saffron's compounds. This approach yielded nanoparticles on the order of 100 nm in diameter containing saffron extract. Importantly, the ultra-small, encapsulated droplets showed a slower release of saffron's bioactives compared to larger particles, which is beneficial for sustained delivery. The nano-emulsified saffron also retained strong antioxidant and antimicrobial efficacy compared with other nanoparticles due to the protected, gradual release of crocin and other components (Safe et al., 2023; Nguyen et al., 2025). Such nanoemulsion systems enable integration of saffron's water-soluble crocin into fat-rich or emulsified food matrices without premature degradation, thereby broadening the range of products that can be fortified with saffron. Another advanced vehicle is nanoliposomes, tiny lipid bilayer vesicles, which have been used to encapsulate saffron's bioactive compounds. Hadavi et al. (2020) optimized nanoliposomal carriers for saffron, demonstrating effective encapsulation of crocin and safranal in vesicles that protect these compounds and potentially facilitate their uptake. Liposomal encapsulation is particularly attractive for saffron because it can improve the dispersibility of both hydrophilic crocin and lipophilic aroma compounds in aqueous food systems, all while shielding them from oxidative damage (Borjizadeh et al., 2024). Additionally, other nanoparticle systems, such as chitosan-alginate nanocomplexes, have been explored for oral delivery of crocin. These biopolymer nanoparticles can be engineered to under 100 nm in size with high encapsulation efficiency (~90% in some formulations), conferring notable stability benefits. For instance, crocin loaded into chitosan/

alginate nanocarriers exhibited much higher stability in simulated gastric conditions, only ~2% degradation at pH = 2 in 1 hour, compared to free crocin, ~7.5% degradation. Such protection in acidic environments is critical for ensuring that saffron's bioactives remain intact during food processing and stomach transit. Overall, emulsion-based micro/nanocarriers and lipid-based nanoparticles represent cutting-edge delivery systems that markedly enhance the stability of saffron constituents and enable their incorporation into diverse functional foods.

The practical outcome of these delivery strategies is the successful development of saffron-enriched functional foods with improved health and product quality. Many staple and specialty foods have been fortified with saffron or its extracts, often with the help of encapsulation techniques to maintain efficacy. Saffron has been added to dairy products (for example, yogurts, cheeses, and milk-based desserts) to boost antioxidant content and impart its characteristic golden color and aroma (Gaglio et al., 2018). Traditional desserts like ice creams, puddings, and pastries have similarly been enriched with saffron to create novel products that marry gourmet appeal with potential health benefits. In baked goods, such as breads, cakes, and cookies, saffron not only contributes to a rich yellow hue and flavor but also increases the antioxidant capacity of the final product, which can prolong shelf life and offer nutritional advantages to consumers (Bhat et al., 2018). Even staple foods like pasta and noodles have been formulated with saffron, yielding pastas with enhanced visual appeal and functional properties due to saffron's bioactives. In each case, formulating saffron requires careful consideration of compound stability. Hence, microencapsulated saffron powders or emulsified extracts are often used to withstand baking or cooking conditions. Saffron's use extends to beverages as well. For example, probiotic fermented drinks and herbal teas have been fortified with saffron extracts to synergistically combine saffron's biofunctional effects, such as mood enhancement and antioxidative activity, with other functional ingredients. A study by Moghaddam et al. (2018) successfully produced a saffron-based probiotic beverage fermented with lactic acid bacteria, illustrating how saffron can be integrated into functional drinks when delivered in a stable form. Overall, these examples underscore that through proper delivery systems, be it encapsulation in a powder, emulsion, or gel form, saffron's valuable compounds can be incorporated into a broad array of functional food products without significant loss of activity. Such saffron-enriched foods provide consumers with added health benefits (antioxidant, anti-inflammatory, etc.) in familiar dietary formats, bridging the gap between culinary tradition and modern nutraceutical innovation.

The critical aim of developing saffron delivery systems is to enhance the stability and bioavailability of crocin and other bioactives throughout processing, storage, and digestion (Nasrpour et al., 2022). Crocin's inherent instability outside the plant matrix means that, in an unprotected state, much of its potency can be lost before it ever confers health benefits. By entrapping crocin within microcapsules or emulsions, the compound is buffered against pH extremes, oxidation, and light exposure that would otherwise cause rapid breakdown. For instance, encapsulated saffron powders can better withstand the thermal stress of baking or pasteurization than free saffron extract, preserving more of the crocin content in the finished product. Moreover, co-encapsulating saffron with natural co-antioxidants or using edible coatings (e.g., nanocellulose or polymer films) can further guard crocin from oxidative degradation during shelf life. In addition to stability, bioavailability, the fraction of an ingested nutrient that is absorbed and utilized in the body, is a key consideration. Notably, crocin glycosides are not readily absorbed intact in the human gastrointestinal tract; they are mainly hydrolyzed into the aglycone crocetin in the intestine, which is then absorbed.

Innovative delivery systems aim to address this by controlling the release and transformation of crocin. Nanoencapsulation, for example, can ensure that crocin is released at a rate and location that optimizes its conversion to crocetin and uptake. In the chitosan/alginate nanoparticle study, the sustained release profile at intestinal pH and the protection in gastric conditions suggest that more crocin could survive to be converted at the absorption site (Rahaiee et al., 2017). The authors noted that the combination of very small particle size, high encapsulation efficiency, and improved stability is expected to enhance crocin's oral bioavailability relative to unformulated crocin. Likewise, liposomal saffron formulations might facilitate direct absorption of lipophilic constituents and improve the mucosal uptake of crocin's metabolites. While more in vivo research is needed, these delivery innovations clearly show potential by shielding crocin and related compounds through the food processing chain and gastrointestinal transit, and by modulating their release, one can achieve a greater bioactive impact from a given dose of saffron.

In summary, the development of delivery systems such as encapsulation (in powders, beads, films), nanoemulsions, and liposomal carriers has become integral to formulating saffron-infused functional foods (Dammak & Conte-Junior, 2023). These technologies effectively preserve saffron's chemical integrity (preventing the loss of crocin, safranal, etc.) and ensure that its health-promoting components are bioaccessible when consumed. As a result, saffron can serve not only as a traditional spice for flavor and color, but also as a reliable functional ingredient in modern food products, provided it is incorporated via smart delivery strategies. The advances in saffron delivery systems and functional formulations thus bridge the gap between the spice's ancient culinary uses and its emerging role as a scientifically validated nutraceutical additive. Each innovation, from microencapsulated saffron powders to saffron-enriched probiotic drinks, contributes to unlocking saffron's full potential while maintaining an academic rigor in ensuring stability, efficacy, and safety in the final edible products. The continuous refinement of these delivery approaches is expected to further improve crocin stability and bioavailability, paving the way for wider utilization of saffron in health-oriented foods and supplements in the future. To highlight the therapeutic relevance and formulation approaches of aqueous saffron extracts in health-promoting products, Table 2 outlines key nutraceutical applications.

Table 2. *Summary of nutraceutical applications of aqueous saffron extracts.*

Application Area	Bioactive Focus	Health Benefit	Formulation Strategies	Supporting Evidence
Cognitive and Mood Disorders	Crocin, safranal	Antidepressant, anxiolytic, cognitive enhancement	Capsules, tablets, encapsulated extracts	Improved mood in clinical trials; enhanced delivery via nanoemulsions
Vision and Eye Health	Crocin, crocetin	Protection against macular degeneration, oxidative stress	Oral supplements, saffron-fortified drinks	Improved retinal function in early-stage AMD trials
Cardiometabolic and Antioxidant Effects	Crocin, phenolic compounds	Antioxidant activity, cholesterol and glucose modulation	Encapsulated powders in dairy, pasta, herbal teas	Reduced lipid peroxidation and improved glycemic control in animal/human studies
Anti-Cancer and Chemoprevention	Crocin, crocetin, safranal	Inhibition of tumor growth, pro-apoptotic actions	Functional food additives, liposomal delivery	In vitro and preclinical data show anti-tumor effects in multiple cancer models
Delivery Systems and Functional Foods	All (especially crocin)	Improved bioavailability and shelf-life	Microencapsulation, hydrogel beads, nanoemulsions in foods	Higher stability in yogurt, bread, and beverages; sustained release in digestion

5. Conclusion

Saffron (*Crocus sativus* L.) holds immense promise as a nutraceutical due to its rich profile of bioactive compounds, particularly crocin, picrocrocin, and safranal, which exhibit potent antioxidant, anti-inflammatory, neuroprotective, and antidepressant properties. However, the practical application of these compounds has long been constrained by their instability and poor bioavailability. Recent advances in aqueous extraction techniques, including ultrasound-assisted, microwave-assisted, enzyme-assisted, and subcritical water extraction, have demonstrated significant improvements in the efficiency, stability, and safety of saffron compound recovery, aligning with green chemistry principles and consumer preferences. These methods not only enhance compound integrity but also support the development of functional food formulations and advanced delivery systems such as microencapsulation, nanoemulsions, and liposomal carriers, all of which help safeguard saffron actives during processing and digestion while improving their absorption. Together, these innovations bridge the gap between traditional medicinal use and modern therapeutic applications, enabling the incorporation of saffron into a diverse range of nutraceutical products with enhanced efficacy. Moving forward, future research must prioritize clinical validation, process scalability, regulatory compliance, and the long-term stability of saffron formulations to fully realize the spice's potential as a scientifically supported functional ingredient.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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