IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

# Different Natural herbs and Medicinal plants as Anticancer Drug, A review

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## Abstract

Cancer poses a significant public health burden in both developed and developing countries, and its treatment often comes with unpleasant side effects such as bone marrow cell destruction and alopecia. As such, there has been increased interest in exploring natural remedies that possess anticancer properties. In this comprehensive review, various Indian medicinal plants from different families with potential anticancer activity are reported. These plants have shown promising results and are candidates for further study and drug discovery. Herbs have been found to play a significant role in cancer prevention and treatment, and this review provides examples of bioactive compounds obtained from these plants. Phytochemical exploration has contributed to the discovery of new anticancer drugs from plants, and people's fear of side effects has led to an increased preference for natural plant products in cancer treatment. The review also highlights diverse methodologies used to evaluate natural compounds for their anticancer potential. Plants have been used for medicinal purposes since the beginning of human history and remain the basis of modern medicine. Several clinically useful anticancer agents have been derived from plant compounds, including vinblastine and vincristine.

Keywords: **Anticancer properties, Medicinal plants, Literature sources, Turmeric, Saffron, Curcumoids, safranal.**

## Introduction

Turmeric, scientifically known as Curcuma longa, is a plant native to South Asia, India, and Indonesia, with a significant portion of its cultivation taking place in South India (2,3). The underground stem, or rhizome, of the plant is crushed and ground into a powder commonly known as turmeric. This spice is used worldwide as a seasoning and as a key ingredient in curry dishes, which contain approximately 2% curcumin - the first curcuminoid to be identified by Miłobędzka et al in 1910 (4). Curcumin is responsible for both the yellow colour of the spice and the majority of the therapeutic effects attributed to turmeric (3,5). Apart from curcumin, turmeric contains various volatile oils (such as zingiberone, atlantone, and tumerone), sugars, resins, and proteins. However, there are no known agents with anti-inflammatory and anti-proliferative activity present in turmeric, other than curcumin (6).

Curcumin, also known as 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene 3,5-dione, has gained significant attention in the scientific community in recent years due to its diverse range of therapeutic properties. This naturally-derived compound is the primary active curcuminoid found in Curcuma longa, an herbaceous perennial plant that belongs to the ginger family, known as Zingiberaceae (1). The other two curcuminoids found in Curcuma longa are desmethoxycurcumin (DMC) and bis-desmethoxycurcumin (BDMC; Fig. 1).

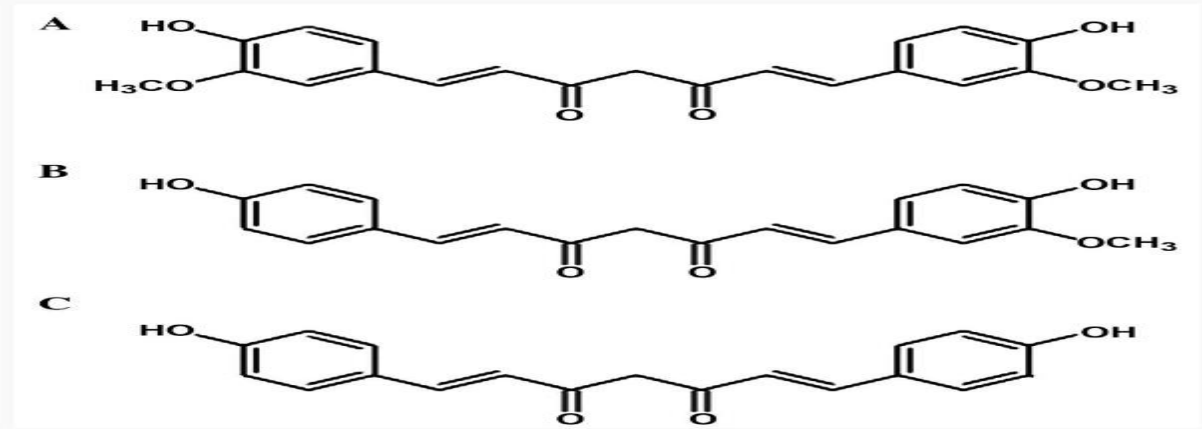


Figure 1. - Primary extracts of the Curcuma longa plant. (A) Curcumin (diferuloloymethane), (B) demethoxycurcumin and (C) bisdemethyoxycurcumin.

Saffron is derived from the dried stigma of the Crocus sativus flower and is believed to possess valuable biological properties [1]. While there is considerable ongoing research on the health benefits of saffron in its natural form [2], significant attention has also been paid to the extraction, purification, and analysis of saffron's major bioactive components, such as crocin, crocetin, picrocrocin, and safranal (Figure 2).

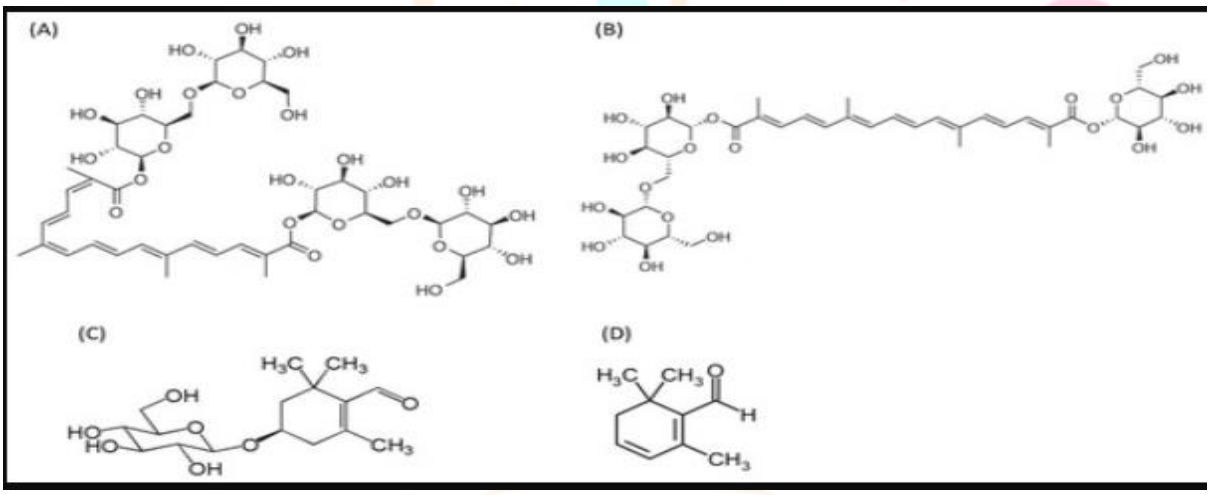


Figure 2. The chemical structure of the four major unique saffron ingredients. (A) Crocin and (B) crocetin are both are water-soluble carotenoid chemical compounds. (C) Picrocrocin is a monoterpene glycoside precursor of safranal (D).

### 1.1 Chemical composition of Curcumoids

Curcumoids are a class of compounds composed of two phenols linked by two α,β-unsaturated carbonyl groups. Curcumin is a terpene-rich compound that contains predominantly monocyclic sesquiterpenes and oxygenated derivatives such as turmerone and zingibrene (17). The rhizome of Curcuma longa, where curcumin is found, contains 3-5% curcuminoids and 2-7% essential oil (18,19). Curcumin is insoluble in water, but it can dissolve in organic solvents like dimethyl sulfoxide, ethanol, methanol, or acetone. Its melting point is 183°C. Curcumin has a maximum spectrophotometric absorption of 430 nm in methanol and 415-420 nm in acetone. A 1% solution of curcumin has 1,650 absorbance units (20).

Saffron, a valuable plant product obtained from the dried stigma of the Crocus sativus flower, is known for its diverse biological properties [1]. While there has been extensive research focused on the health benefits of saffron in its natural form [2], attention has also been paid to the extraction, purification, and analysis of saffron's major bioactive constituents, including crocin, crocetin, picrocrocin, and safranal (Figure 1), which have been found to exhibit beneficial effects against a range of diseases such as diabetes [3], neurodegenerative and cognitive disorders [4], depression [5], inflammatory and autoimmune diseases [6,7], digestive issues [8], and cardiovascular inflammation [9].

In addition, saffron and its components have been investigated for their potential anticancer activity in preclinical settings [10]. Significantly, saffron has been shown to have potent anticancer activity without any adverse effects on normal cells [11,12]. However, despite the extensive research, the precise mechanisms underlying saffron and its components' actions against cancer progression remain largely unknown. It is suggested that saffron and its major components may have a pleiotropic mechanism of action against malignant cells. Numerous studies have explored the effect and mechanism of action of different saffron extract ingredients and how their action can be optimized [13,14]. Additionally, saffron's major ingredients may act synergistically against malignant cells, highlighting the potential for saffron extract to be more effective than its individual components [15]. It is worth noting that saffron contains other bioactive compounds, such as kaempferol and its glycosides, quercetin, and other flavonols [16].

### 1.2 Anti-inflammatory activity of Curcumoids

Studies at the molecular level have shown that curcumin can prevent the activation of certain factors or enzymes in human cells that trigger inflammatory responses. For example, researchers have discovered that curcumin can block the activity and expression of cyclooxygenase-2 (COX-2) in various cell lines and animal models (21,22). When applied topically, curcumin can also inhibit the induction of COX-2 expression by lipopolysaccharides (LPS), which reduces the formation of prostaglandin E2 (PGE2) but increases the levels of COX-2 in macrophages that are not stimulated by LPS (23). Additionally, curcumin has been shown to suppress the expression of COX-2 protein and mRNA, as well as the production of PGE2 induced by various factors, such as TPA or chenodeoxycholate (24). Curcumin also reduces the levels of COX-2 and PGE2 synthase 1, which are involved in PGE2 formation and play a crucial role in inflammation and tumor development. Moreover, curcumin can reversibly inhibit the conversion of prostaglandin H2 (PGH2) to PGE2 by microsomal PGE2 synthase 1 in A549 lung cancer cells stimulated with interleukin (IL)-1β (25). In human whole blood stimulated with LPS, curcumin inhibits the formation of PGE2 by COX-2 from arachidonic acid (AA), while the formation of other compounds such as 6-keto PGF2α and 12 (1)-hydroxy-5-cis-8,10-transeptadecatrienoico by COX-1 is suppressed only at higher concentrations (26). It has been suggested that the deletion of microsomal PGE2 synthase 1 by curcumin is important for its anti-inflammatory and anticancer effects (26).

However, curcumoids have been found to significantly inhibit the peroxidase activity of COX-1, but not that of COX-2. In addition, curcumin and other curcumoids can markedly inhibit the activity of 5-lipoxygenase (5-LOX) by blocking cytosolic phospholipase A2 phosphorylation, which interferes with the metabolism of AA, reduces the expression of COX-2, and inhibits the catalytic activities of 5-LOX. These activities may explain the anti-inflammatory effects of curcumin and other curcumoids in general (23).

### 1.3 Effect on arthritis of Curcumoids.

Curcumin has long been utilized in Ayurvedic medicine for the treatment of inflammatory conditions such as arthritis and is often taken as a dietary supplement. Research conducted by Funk et al (36) found that an extract lacking essential oils was effective in preventing joint inflammation. Additionally, a hydroalcoholic extract of turmeric was shown to inhibit joint inflammation and tissue destruction in a dose-dependent manner (37). Recent studies have indicated that oral administration of curcumin can reduce the neutrophil inflammatory response in rats with zymosan-induced arthritis (38). Moreover, Panahi et al suggested that treatment with curcuminoids offers a safe and effective alternative for the management of osteoarthritis (39).

### 1.4 Antiplatelet activity of Curcumoids

Curcumin, a compound found in turmeric, has been shown to have anti-thrombotic effects both in vitro and ex vivo. Specifically, it inhibits the production of thromboxane (TX) by platelets and increases fibrinolysis, while also inhibiting platelet aggregation induced by ADP, collagen, or norepinephrine. Unlike aspirin, curcumin does not decrease the synthesis of prostacyclin in the aortic arch epithelium, but instead, its action on prostacyclin increases with progressively higher doses of curcumin, providing protection against collagen or norepinephrine-induced thrombosis. The hydroalcoholic extract of turmeric has also been found to inhibit platelet aggregation induced by AA, increase fibrinolysis, inhibit the production of TX by exogenous AA, and inhibit the release of AA, possibly through the inhibition of TX synthase. However, the essential oil of turmeric does not exhibit anti-platelet activity. Interestingly, a combination of curcumin and clopidogrel, a drug from the antiplatelet family of

thienopyridines, did not have a significant effect on the maximum platelet aggregation rate in rats when compared with the use of clopidogrel alone.

### 1.5 Antioxidant activity of Curcumoids

The chemical composition of curcuminoids provides them with antioxidant properties. Curcumin is capable of inhibiting lipid peroxidation of linoleate, a polyunsaturated fatty acid that can form fatty acid radicals when oxidized. These compounds also function as NO scavengers by blocking the enzyme responsible for its synthesis, which results in a promoter activity. Curcuminoids also exhibit marked reductions in erythrocyte hemolysis and lipid peroxidation, and they reduce vitamin E levels. NO is a lipophilic molecule that has a short half-life, and it is produced from L-arginine by various NO synthases that are NADPH-dependent. NO plays a role in vasorelaxation, neurotransmission, platelet aggregation inhibition, immunity, and intracellular signaling. Curcumin has also been investigated for its potential use in preventing neurodegenerative diseases, such as Alzheimer's disease. Because oxidative damage and inflammation are elevated in the brains of Alzheimer's patients, turmeric's aqueous extract can be used in long-term therapy to reduce and prevent oxidation.

### 1.6 Anticancer activity of Curcumoids

Curcumin has shown potential as an anticancer agent, with both chemopreventive and therapeutic effects. While most studies on this topic have been conducted on animal models, comparable dosages have been shown to be effective in various in vitro models. Curcumin's ability to prevent carcinogenesis is attributed to its impact on two primary processes: tumor growth and angiogenesis (32).

Turmeric and curcuminoids have been found to affect tumor angiogenesis through multiple interdependent mechanisms (33). These include: i) modulation of transcription factors NF-κB, AP-1, and early growth response protein 1, which in turn inhibits the expression of IL-8 in pancreatic and head and neck cancer cells, and prevents VEGF synthesis; ii) inhibition of angiogenesis mediated by NO and iNOS; iii) inhibition of COX-2 and 5-LOX; iv) modulation of angiogenic factors such as VEGF and basic fibroblast growth factor; and v) improvement of extracellular matrix stability and coherence, which involves downregulation of MMP-2 and MMP-9, and upregulation of tissue inhibitor of metalloproteinase-1. Turmeric also hinders the release of angiogenic factors that are stored in the extracellular matrix (44).

Cancer is characterized by an imbalance between cell proliferation and cell death due to the absence of apoptotic signals, resulting in uncontrolled cell growth. Apoptosis can be induced through two major pathways, the intrinsic and extrinsic pathways. The intrinsic pathway works by suppressing anti-apoptotic proteins Bcl-2 and Bcl-Xl through stimulation of the mitochondrial membrane. Curcumin can disturb the balance of the mitochondrial membrane potential, leading to enhanced suppression of Bcl-Xl. The extrinsic pathway increases the expression of death receptors (DRs) and triggers tumor necrosis factor-related apoptosis. Curcumin upregulates the expression of DR4 and DR5 to contribute to this pathway.

In vitro studies have demonstrated that curcumin and its derivatives have the ability to induce apoptosis in different cell lines by inhibiting or downregulating various intracellular transcription factors, such as NF-κB, AP-1, COX-2, nitric oxide synthase, MMP-9, and STAT3. Additionally, recent research has identified a new mechanism for the anticancer effects of curcumin by decreasing glucose uptake and lactate production (Warburg effect) in cancer cells through the downregulation of PKM2. The inhibition of PKM2 is achieved by suppressing the mammalian target of rapamycin-hypoxia-inducible factor 1α (TOR-HIF1α).

Several studies have explored the ability of curcumin and its derivatives to suppress multiple carcinomas by interacting with various molecular targets, as illustrated in Figure 3.

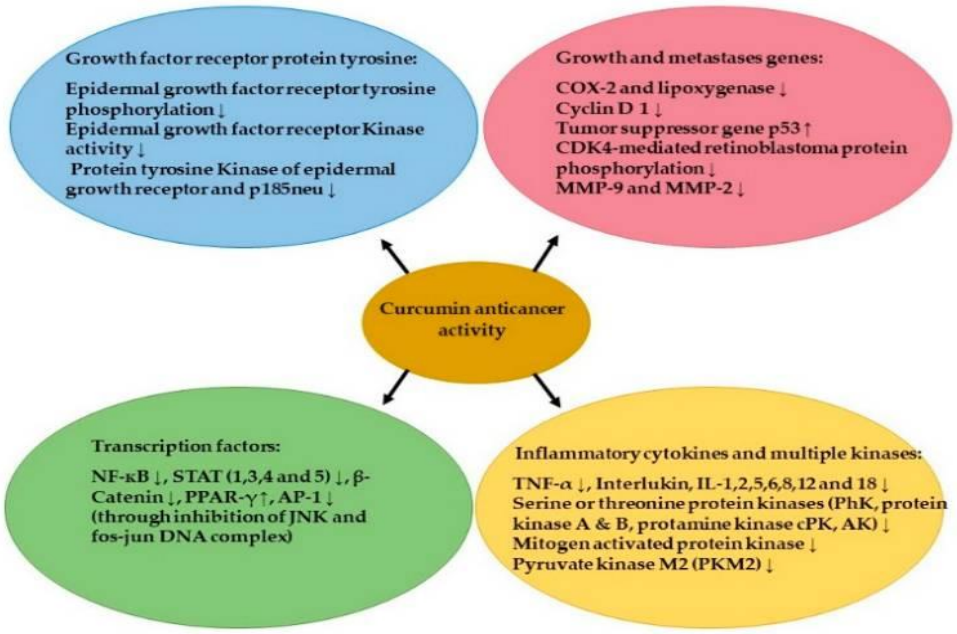


Figure 3. The main molecular targets of curcumin in cancer cells. ↑: Increase; ↓: Decrease; MMP: Matrix metalloproteinase; AP-1: Activation protein-1.

### 1.7 Prostate Cancer

According to recent estimates by the American Cancer Society, prostate cancer (PCa) has been diagnosed in 2.9 million men in the United States, making it the second leading cause of cancer death in men. Curcumin has shown potent anti-proliferative and pro-apoptotic effects on prostate cancer both in vitro and in vivo, through its interference with several cellular pathways including MAPK, EGFR, and NFκB. Recent studies have revealed that curcumin can activate protein kinase D1 (PKD1), thereby attenuating the oncogenic signaling by β-catenin and MAPK and inhibiting prostate cancer. PKD1 was found to be significantly downregulated in androgen-independent prostate cancer and affects the motility and invasion of prostate cancer through interaction with E-cadherin, making it a promising therapeutic target for prostate cancer. Apart from curcumin, its derivatives have also exhibited potent anticancer activity against prostate cancer. Metallo-curcumin conjugated DNA complexes demonstrated significant toxicity to prostate cancer cells, while Dimethyl curcumin (ASC-J9) showed excellent activity in enhancing androgen receptor degradation in androgen-dependent prostate cancer.

### 1.8 Colorectal Cancer

Colorectal cancer ranks as the third most common malignant cancer after lung and prostate cancers [41]. Despite undergoing surgical removal of the tumor tissue along with chemotherapy, over half of colorectal carcinoma patients suffer from relapses [36]. Curcumin has been found to reduce M (1) G levels in malignant colorectal cells without altering COX-2 protein levels [38]. Additionally, curcumin has been shown to downregulate the miR-21 gene, which is overexpressed in colorectal cancer cells, by inhibiting the activator protein (AP-1) binding to the miR-21 promoter [45]. Treatment of HCT 116 colorectal cancer cells with curcumin resulted in cell cycle arrest in the G2/M phase via miR-21 gene regulation and inhibited tumor tissue growth [15]. Furthermore, an in vivo study in mice with colorectal cancer demonstrated that curcumin improved response to radiation therapy due to its ability to target nuclear factor (NF-κB) [18]. Another study has enhanced curcumin's inhibition activity against colon cancer cells by combining it with ERRP, a pan-erb B inhibitor [29].

### 1.9 Head and Neck Squamous Cell Carcinoma

Head and neck squamous cell carcinoma (HNSCC) is a prevalent form of cancer, affecting more than 30,000 people worldwide every year, and ranks as the sixth most common cancer [19]. Typically arising in the oral cavity, paranasal cavities, larynx, and pharynx, HNSCC can be challenging to treat effectively. However, in vitro studies have demonstrated the potential of curcumin to inhibit cell growth in different head and neck cancer cell lines by targeting several cellular pathways involved in cell proliferation, particularly NF-κB and STAT3, which are

commonly overexpressed in various head and neck carcinomas [10,11]. Specifically, curcumin has been found to downregulate NF-κB and inhibit the interleukin-6 (IL-6)-mediated phosphorylation of STAT3, thus effectively hindering the proliferation of cancer cells [11,12].

### 1.10 Liver cancer

Curcumin has shown promise as a potential treatment for liver cancer. In animal studies, it has been shown to inhibit the development of hepatic hyperplastic nodules, prevent hypoproteinemia, and reduce body weight loss in Wistar rats (14). Additionally, in a study using C3H/HeN mice, which were injected with the powerful hepatocarcinogen N-nitrosodimethylamine (DENA), mice that received a diet containing 0.2% curcumin had an 81% reduction in the multiplicity and a 62% reduction in the incidence of hepatocarcinoma compared with the non-treated group after 42 weeks (14). Another study by Busquets et al. evaluated the chemopreventive potential of curcumin in rats that were inoculated with the fast-growing tumor, Yoshida AH-130 ascites hepatoma, and found that curcumin significantly decreased tumor growth by 31% (15).

### 1.11 Skin carcinogenesis

In female CD-1 mice, topical application of curcumin combined with the tumor promoter TPA twice a week for 20 weeks resulted in significant inhibition of papilloma formation (66). Moreover, in another study, relatively low doses of curcumin (20 or 100 nmol) topically applied had remarkable preventive effects against TPA-induced tumor promotion. Whether applied topically as a commercial-grade curcumin, pure curcumin or demethoxycurcumin, they showed almost similar inhibitory effects on TPA-induced tumor promotion in DMBA-initiated mouse skin carcinogenesis. Additionally, dietary administration of 2% turmeric in female Swiss mice significantly suppressed DMBA and TPA-induced skin tumor formation. In a benzo[a]pyrene-initiated and TPA-promoted two-stage skin tumorigenesis model, curcumin administration reduced the number of tumors per mouse and the number of tumor-bearing mice. Furthermore, curcumin was also shown to inhibit UV-induced dermatitis in mouse skin in several studies conducted by Huang et al (67-69).

### 1.12 Pancreatic cancer

In a study using a xenograft model, female nude mice were injected subcutaneously with pancreatic cancer cells on the side of their abdomen (17). Afterwards, liposomal curcumin was injected into the mice which resulted in reduced tumor size and a decrease in the expression of CD31, VEGF, and IL-8. This suggests that curcumin can suppress pancreatic carcinoma growth and inhibit tumor angiogenesis in murine xenograft models (17).

Bao et al found that the administration of difluorinated-curcumin (CDF) was able to inhibit tumor growth by reducing the expression levels of EZH2, Notch-1, CD44, EpCAM, and NANOG, and increasing the expression levels of let-7, miR-26a, and miR-101, which are not typically expressed in pancreatic cancer (18).

### 1.13 Prostate cancer

In a study, mice were fed with a diet containing 2% curcumin and subcutaneously injected with androgen-dependent LNCaP prostate cancer cells for up to 6 weeks (25). The administration of curcumin resulted in a significant increase in apoptosis, as indicated by an in situ cell death assay, and a decrease in cell proliferation, as measured by a BrdU incorporation assay (26). Additionally, curcumin was found to significantly decrease the activity of MMP-2 and MMP-9 in tumor-bearing sites. In a previous study, the curcumin-treated group showed significantly fewer metastatic nodules compared to the untreated group (25).

### 1.14 Ovarian cancer

A study was conducted to assess the efficacy of curcumin against ovarian cancer, where animals were treated with curcumin alone or in combination with docetaxel (26). Curcumin treatment alone led to a reduction of 49–55% in mean tumor growth compared to control animals, while the combination of curcumin with docetaxel resulted in a 77% reduction in mean tumor growth compared to the controls. Both treatments induced a decrease in proliferation and microvessel density and a significant increase in tumor cell apoptosis (38). In a recent in vitro study, it was

demonstrated that the combination of curcumin and triptolide synergistically inhibited the growth of ovarian cancer cells (27).

### 1.15 Lung cancer

In an animal study, curcumin administration reduced the number of lung tumor nodules and inhibited the metastasis of melanoma to the lungs, indicating its potential as a treatment for metastatic tumor growth. Curcumin was also found to inhibit cigarette smoke-induced NF-κB activation in lung cells, which led to a reduction in the expression of cyclin D1, COX-2, and MMP-9, all of which are associated with tumor growth and metastasis. Yang et al (40) demonstrated that curcumin inhibits cell proliferation by modifying the expression of proliferative and anti-proliferative proteins, including survivin, Bcl-XL, and cyclin B1. Curcumin also affects cell cycle, migration, and invasion, and reduces angiogenesis through suppression of the STAT3 signaling pathway in small cell lung cancer.

### 1.16 Head and neck cancer

Male F344 rats were administered curcumin (0.5 g/kg) resulting in a 91% reduction in the frequency of 4-nitroquinoline 1-oxide-induced tongue carcinoma and a marked reduction in the incidence of oral preneoplastic lesions (41). In another study, Azuine et al (42) used a Syrian golden hamster model to demonstrate that curcumin, either alone or in combination with catechin, inhibited the development of methyl(acetoxymethyl)nitrosamine-induced oral mucosal tumors. Treatment with 10 mmol curcumin also resulted in a 39.6% reduction in visible oral papillomas and a 61.3% reduction in papilloma volume (42). Furthermore, curcumin administration reduced the incidence of oral squamous cell carcinoma, with the number of oral SCC lesions decreasing by 51.3% (30). After curcumin treatment, a reduction in the tumor proliferation index was observed in hyperplasia, dysplasia, and papilloma (43).

## PART 2: Anticancer Properties of Saffron and Its Major Ingredients

### 2.1 ANTICANCER ACTIVITY OF SAFFRON

in lifestyle and increased longevity have led to a higher incidence of cancer. The World Health Organization (WHO) has declared cancer to be a major cause of death and morbidity in the human population (Globocan, 2016), with the International Agency for Research on Cancer (IARC) reporting an increase in cancer deaths from 7.4 million in 2004 to 8.2 million in 2012 (Globocan, 2016) [7]. Urbanization, industrialization, lifestyle changes, and an aging population are among the factors contributing to the increasing incidence of cancer (Zanardi et al., 2016).

Current treatments for cancer, such as radiotherapy and chemotherapy, have various side effects and are not always effective. As a result, there has been increasing interest in alternative medicines, and traditional knowledge has been utilized in the development of new effective medicines. Many common Indian spices and herbs used in Indian ayurvedic medicine, including ginger, turmeric, cumin, basil, and saffron, are known to have anti-cancer potential (C.M. Kaefer and J.A. Milner, 2011). Therefore, research on natural compounds such as these may hold promise for the development of new treatments for cancer that are safer and more effective.

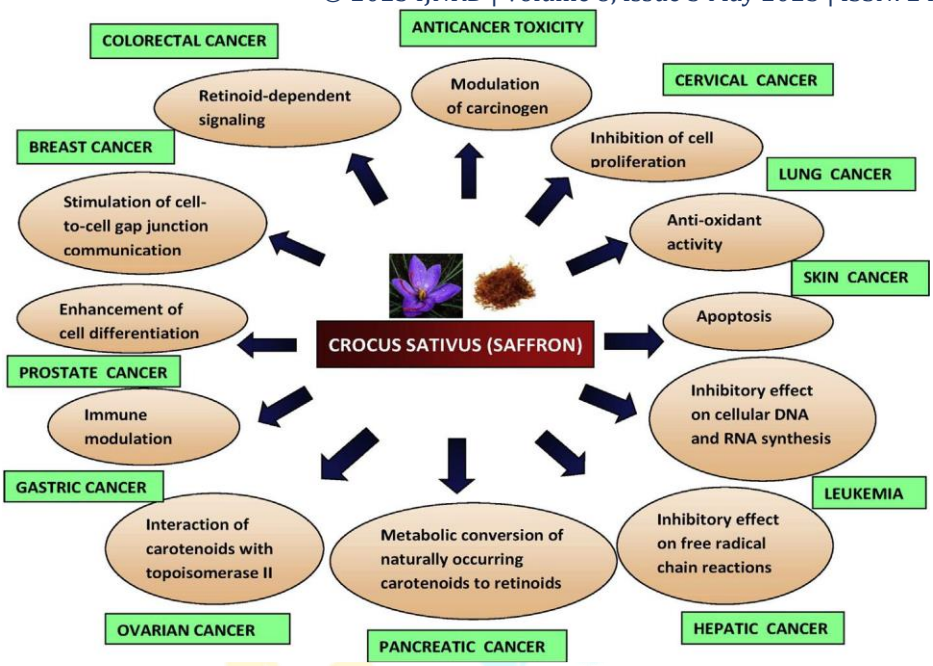


Figure 4: CROCUS SATIVUS ANTICANCER MACHANISMS

### 2.2 Effects of Saffron towards Preventing Carcinogenesis

Scientists dedicate a considerable amount of effort to identifying molecules that can delay the development of carcinogenesis in its earliest stages or even reverse cancer growth. With this goal in mind, studies have shown that saffron extract can prevent the formation of tumors at an initial stage. In a recent investigation on hamsters exposed to the carcinogen 7,12-dimethylbenz[a]anthracene (DMBA), oral administration of saffron at a dosage of 100 mg/kg b.w./day one week before exposure to the carcinogen completely prevented the development of oral squamous cell carcinomas [47]. Similarly, in mice that received three topical applications of 100 nmol DMBA in 100 mL acetone, the ingestion of 200 mg/kg b.w./day saffron delayed the onset of skin papilloma formation [46].

### 2.3 Saffron and Its Components as Anticancer Agents

Saffron and its components have shown significant antitumor properties in both in vitro and in vivo studies. However, researchers are still working to determine the specific mechanism of action of each saffron component against cancer. The antitumor activity of saffron is believed to be primarily due to: (i) the inhibition of DNA and RNA synthesis, (ii) the inhibition or suppression of cancer cell proliferation, (iii) the induction of apoptosis, (iv) the inhibition of metastasis and angiogenesis, and (v) alterations in the expression of oncogenes or tumor suppressor genes.

### 2.4 Breast Cancer

In various studies, saffron and its constituents have shown potential antitumor effects. Mousavi et al. found that saffron ethanol extract induced apoptosis and decreased MCF-7 cell viability with an IC50 of 400 ± 18.5 µg/mL after 48 hours via caspase activation and Bax increment [19]. Another study by Mousavi and Baharara demonstrated the inhibitory effect of saffron aqueous extract on the expression of two biomarkers of angiogenesis, VEGF-A and VEGFR-2, in the MCF-7 cell line [50].

Saffron constituents, including trans-crocin-4, crocetin, and safranal, have also been found to inhibit the proliferation of MCF-7 and MDA-MB231 cells [71]. Trans-crocin-4 and crocetin inhibited the proliferation of both cell lines at concentrations higher than 200 µM, while safranal inhibited the proliferation of MDA-MB231 at concentrations higher than 125 µM and MCF-7 at concentrations higher than 500 µM. Crocetin was also found to inhibit invasiveness by reducing the expression of matrix metalloproteases and induce apoptotic DNA fragmentation in electrophoresis in MCF-7 cells [68]. However, further research is still required to determine the exact mechanism of action of these saffron components in cancer treatment.

### 2.5 Ovarian Cancer

In a study by Xia et al., the effect of crocin on the human ovarian cancer cell line HO-8910 was investigated. The results showed that crocin inhibited the growth rate of the cells and increased the proportion of HO-8910 cells in the G0/G1 phase, leading to an increase in apoptosis rate. Crocin was also found to upregulate the expression of p53 and Fas/APO-1, which subsequently activated the apoptotic pathway through caspase 3 activation [55].

### 2.6 Gastrointestinal Cancer

Numerous studies have investigated the potential anticancer effects of saffron and its components on gastrointestinal cancer, including colorectal cancer [46,47,48,49,50,61,62,63]. Specifically, crocin has been shown to induce apoptotic cell death in colorectal cancer cells through both p53-dependent and -independent mechanisms [50,62].

Recent research has reported on the anticancer activity of crocin against three human colorectal cancer cell lines (HCT-116, SW-480, and HT-29). Crocin effectively reduced the rate of cell proliferation, with HCT-116 cells exhibiting greater sensitivity to crocin compared to the other two cell lines. The results suggest that the sensitivity of HCT-116 cells to crocin is attributed to the presence of wild-type p53, whereas SW-480 and HT-29 cells have a mutant p53 tumor suppressor gene, indicating a potential link between the anticancer activity of crocin and p53 expression [50,71].

### 2.7 Lung Cancer

In a study by Chen et al., the effect of crocin was investigated on two human lung cancer cell lines, A549 and SPC-A1 [51]. Crocin was found to inhibit cell proliferation and induce apoptosis in a concentration-dependent manner, which was accompanied by an increase in G0/G1 arrest. Furthermore, crocin was found to increase the mRNA levels of p53 and B-cell lymphoma 2-associated X protein (Bax), while it decreased the mRNA expressions of B-cell lymphoma 2 (Bcl-2). The study also revealed that when crocin was combined with cisplatin or pemetrexed, it had a stronger inhibitory effect than the single agent. Therefore, these findings suggest that crocin could be used in combination with these chemotherapeutic agents for the treatment of lung cancer.

### 2.8 Leukemia

Studies have investigated the potential cytotoxic effects of crocetin on various leukemia cancer cell lines, including HL60, K-562, L1210, NB4, and P388, through in vitro experiments [52]. Moradzadeh et al. explored the apoptotic potential of crocetin and its underlying mechanism in acute human leukemia HL-60 cells in comparison to normal human polymorph nuclear (PMN) cells [53]. The findings suggested that crocetin can decrease cell viability and increase sub-G1 cell population in HL-60 cells in a concentration-dependent manner without significant toxicity towards normal PMN cells. Moreover, the expression of caspase 3, 9, and Bax/Bcl-2 ratio significantly increased in HL-60 cells, while caspase 8 remained unchanged. The researchers suggested that crocetin promoted apoptosis through the induction of the intrinsic pathway. Crocetin's efficacy was compared with that of ATRA (all-trans-retinoic acid), an anticancer chemotherapy drug, and arsenic trioxide (As2O3), which have therapeutic effects on leukemia. However, the high toxicity of ATRA and As2O3 remains a significant limitation for their use at high therapeutic doses. Therefore, crocetin may serve as an appropriate alternative drug against leukemia.

### 2.9 Use of Saffron Ingredients as Adjuvants to Chemotherapeutic Drugs

In addition to the conventional methods of cancer treatment, including radiotherapy, chemotherapy, immunotherapy, and surgery [55], researchers are exploring alternative approaches to improve the quality of life of cancer patients. Saffron compounds have been found to be a safe and effective treatment for reducing the toxic side effects of some traditional chemotherapeutic drugs such as tamoxifen [54,59], cisplatin [55], and doxorubicin [56]. Furthermore, in addition to the protective properties described earlier, several studies have demonstrated that combining saffron extracts with chemotherapeutic drugs can have synergistic effects, enhancing the effectiveness of the treatment. For instance, a synergistic antiproliferative and apoptotic effect of crocin and cisplatin has been observed in human osteosarcoma and lung cancer cells [58,63]. Saffron pretreatment has been found to significantly inhibit DNA damage (strand breaks) caused by antitumor drugs like cisplatin, cyclophosphamide, and mitomycin-C, and protected normal cells against the genotoxicity of these antitumor drugs [59,68].

### 2.10 Clinical Trials

Numerous studies have investigated the anticancer properties of saffron and its unique constituents, including crocin, crocetin, and safranal. Preclinical studies have shown that these substances selectively target malignant cells while sparing normal cells, making them ideal for developing human therapeutic approaches. However, despite promising results from preclinical studies, little research has been conducted on human subjects. Only two clinical trials have reported the use of saffron for cancer treatment. One clinical study published in the Avicenna Journal of Phytomedicine (AJP) demonstrated the anticancer effect of saffron in combination with chemotherapy in 13 cancer patients suffering from liver metastasis[72]. These patients had primary cancer of the esophagus, stomach, colon, ovary, or breast and consumed capsules containing 50 mg of dried saffron stigma. The treatment's efficacy was evaluated based on CT scan results, and 14.3% of the group showed a complete response to saffron treatment. Although this is an important outcome towards establishing the proof-of-concept for the anticancer properties of saffron, a larger sample size is required, as the placebo and saffron groups included only three and four patients, respectively.

## Conclusion

Curcumin, also known as diferuloylmethane, is a polyphenol obtained from Curcuma longa that possesses various therapeutic properties such as anti-inflammatory, antioxidant, antiseptic, and analgesic activities. Numerous studies have recently suggested the anticancer properties of curcumin by examining its effects on a range of biological pathways involved in mutagenesis, apoptosis, tumorigenesis, cell cycle regulation, and metastasis. The outcomes reviewed in this study demonstrate that curcumin may have beneficial effects against various types of tumors. Of note, researchers have combined curcumin with other nutraceuticals, including resveratrol, to target the mechanisms behind tumorigenesis, and studies have shown that curcumin analogues can serve as promising treatments for cancer. Therefore, additional in vivo studies that shed light on the mechanisms underlying the effects of this nutraceutical could prove valuable in treating tumors and eliminating the need for cancer treatments that come with known side effects.

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