Modulatory Properties of Curcumin in Cancer: The Role of Interferons

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Funding: None.

Conflict of interests: None.

Abstract

The immune network is an effective network of cell types and chemical compounds established to maintain the body's homeostasis from foreign threats and to prevent the risk of a wide range of diseases; hence, its proper functioning and balance is essential. A dysfunctional immune system can contribute to various disorders, including cancer. Therefore, there has been considerable interest in molecules that can modulate the immune network. Curcumin, the active ingredient of turmeric, is one of these herbal remedies with many beneficial effects, including modulation of immunity. Curcumin is beneficial in managing various chronic inflammatory conditions, improving brain function, lowering cardiovascular disease risk, prevention and management of dementia, and prevention of aging. Several clinical studies have supported this evidence, suggesting curcumin to have an immunomodulatory and anti-inflammatory function; nevertheless, its mechanism of action is still not clear. In the current review, we aim to explore the modulatory function of curcumin through interferons in cancers.

Keywords: Curcumin; Immunomodulation; Cancer; Turmeric

Introduction

Immune System functions

The immune network of the human body comprises of several different components including cells, tissues, organs, and proteins that interact with each other and plays an important role in protecting the body against external invaders such as bacteria, viruses, fungi, and toxins produced by microbes. One of the remarkable features of this network is its property of distinguishing non-self-cells (foreign) from what is self (the body's normal cells). Dead and defective cells are also identified and removed by the immune system. The immune network comprises of two distinct parts: innate immunity and acquired immunity, each of them playing an entirely different role in initiating immune system response. The body's first level of defense is the innate immune system or natural immune system, which includes cells that generally find and kill pathogens in the body. The response produced by the innate immune system is not specific and stable (without memory cells), affects a wide range of microbes, and does not result in immunity (Marshall et al., 2018). This innate immunity consists of diverse components, including physical barriers, phagocytic cells, complement proteins and cell receptors, such as toll-like receptors (TLRs). TLRs belong to a group of receptors called Pattern recognition receptors (PRPs) that are proteins used by the innate immune network cells to identify pathogens-associated molecular patterns (PAMPs). The famous examples of PAMPs are peptidoglycan and lipoproteins generated by palmitoylation of the N-terminal cysteines of many bacterial cell wall proteins, lipoteichoic acids (LTA) of gram-positive bacteria and lipopolysaccharide (LPS) of gram-negative bacteria (Weber, 2014). Although there are exceptions, pattern recognition receptors enable innate immune cells to detect foreign cells on their own, but these cells cannot discriminate among different foreign cells (Ueta and Kinoshita, 2010). In contrast, the adaptive immune system, also known as acquired immunity, uses unique antigens to provide an immune response. Adaptive immunity is triggered by pathogens exposure, and unlike innate immunity, it has an immunological memory that enables it to produce a stronger and faster response to pathogen re-exposure (Iwasaki and Medzhitov, 2015). The innate immune system detects the foreign antigens and delivers them to the adaptive system through the major histocompatibility complex (MHC) proteins. The innate cells also produce other chemical signals, including chemokines and cytokines, to stimulate the adaptive immune system. In addition to these, regulatory cells are also a part of the immune system that suppresses the immune responses of other cells. This is an essential "self-check" developed

into the immune system to avoid over-reaction (Josefowicz et al., 2012; Mauri and Bosma, 2012). Components of adaptive and innate immunity are shown in **Figure 1**.

Interferon family

Host cells produces chemicals called interferons (IFNs) as response to reaction induced against various invading antigens. IFNs belong to a broad category of proteins identified as cytokines, which are molecules used for cell-to-cell interaction that activate immune systems which in turn help in eliminating pathogens. Usually, they are categorized into three classes: interferon I, II, and III.

Generally, the two crucial type I IFNs are IFN-α and IFN-β and further other isotypes, as IFN-δ, IFN-ε, IFN-κ, IFN-τ and IFN-ω. This form of cytokines has the same structure, binds to a similar cellular receptor, and is encoded by a family of related genes presented on human chromosome 9 (Parham, 2014; Kopitar-Jerala, 2017). IFN I family synthesis is prompted when PRRs are exposed to microbial challenges such as viral, bacterial infection, or microbial nucleic acid. These receptors are found in the cytosol or the endosome. If the virus attacks the cell, the cell triggers signals that contribute to phosphorylation, dimerization and passage to the nucleus of the interferon response factor 3 (IRF3). In addition to IRF3, different transcription factors, such as nuclear factor kappa B (NF-κB) and activating protein 1 (AP-1), initiate the transcription of the IFN-β gene. Subsequently, the produced IFN-β binds to the interferon receptor (IFNAR), which is located on the surface of the infected cell, leading to autocrine signaling to activate other IFN response factors and modifying gene expression patterns to provide IFN reactions. IFN-β also binds to its receptors in non-virus-infected neighboring cells, interacting in a paracrine manner to prevent these cells from being infected with viral infection (Abbas et al., 2015; Haller et al., 2006; Ronnblom, 2016). Many cells such as the endothelial cells, fibroblasts and leukocytes secrete IFN-α and IFN-β. Additionally, DCs also known as the normal "IFN-producing cells" (IPCs) specializes in the rapid secretion of large amounts of interferons. During a viral challenge, these cells produce up to a thousand times more interferon than other cells.

In addition to being a primary protector against viral infections, IFNs play a significant role in immune surveillance for malignant cells. In particular, IFN-α and IFN-β exhibit potent antiviral activity. The interferons IFN-α and IFN-β generally have three main functions. Primarily, in the initial stage, activating the cellular genes which results in the destruction of virus mRNA

and inhibition of the translation of viral proteins, helps in preventing virus replication in cells. Furthermore, they stimulate the response of ligands to NK cell receptors expression in infected cells eventually, causing the NK cells to eliminate virus-infected cells (Platanias, 2005; González-Navajas et al., 2012; Stackaruk et al., 2013).

IFN-γ is the most important type of IFN II cytokine. One of the main functions of these cytokines is to activate macrophages in innate and adaptive immune responses. Unlike IFN type I, the IFN-γ is encoded by chromosome 12. Although IFN-γ is a member of the interferon family, it does not have a strong antiviral function. The primary role of IFN-γ is to activate effector cells in the immune system. In adaptive immunity, IFN-γ is secreted as a result of antigen recognition by T cells. In addition, its production is stimulated by IL-12 and IL-18. In addition to these cytokines, B-lymphocytes and professional antigen-presenting cells such as monocytes, macrophages and dendritic cells (DCs) are also involved in the development of IFN-γ. Unlike IL-12 and IL-18, which stimulate interferon synthesis, IL-4, and IL-10, are considered to be inhibitory regulators of interferon type 2 production (Ivashkiv, 2018; Abbas et al., 2015).

IFN type III are a class of cytokines consisting of four subtypes, IFN-λ1, IFN-λ2, IFN-, and IFN-λ4. These cytokines, similar to the type I interferons, have antiviral activity. Moreover, the signaling pathway for type III interferons is identical to that of type I, including the processes that depend on IRFs and NF-£B activities. NF-£B plays a critical role in the control of IFN type III expression. However, the expression of IFN-λ is more flexible than type I interferons, as it also involves independent actions of NF-kB and IRFs that induces the production of cytokines in response to a variety of stimuli. Viruses, as well as certain microbial-derived products, increase the expression of IFN-λ. Also, all types of cells, mainly pDCs, produce iIFN-λ following viral infection. Nevertheless, macrophages are not included in IFN-λ development, unlike the other forms of IFN. With regard to bioactivities, besides controlling innate and adaptive immune responses, IFN-λ works as the first phase of immunity against viral infections. In recent studies, a new group of interferon-type 3 cytokines was rapidly produced in HCV-infected primary human hepatocytes. This cytokine, which has strong antiviral properties, was called IFN-λ4. IFN-λ can have potent antiviral activity against several viruses without additional undesired pro-inflammatory effects of type I IFNs (Ank et al., 2006; Iversen and Paludan, 2010; O'Brien et al., 2014; Kotenko and Durbin, 2017).

Methods

We reviewed studies that examined the modulatory properties of curcumin in different cancer such as breast, lung, melanoma, pancreatic and colorectal cancer, through regulating the expression of cytokines, especially interferons. Until June 2022, we searched databases such as PubMed, Google Scholar, Scopus, Ovid-Medline, and Web of Science, with no restrictions on the course, language, or type of work. Therefore, case studies, clinical trials, original research, were evaluated. We use free text as well as Medical Subject Heading (MeSH) terms "Curcumin," "Cancer", "Cytokines", "Interferon", "Breast cancer"," Lung cancer"," Melanoma", "Pancreatic cancer", "Colorectal cancer", "signaling pathways".
Some studies based on inclusion and exclusion criteria were excluded from our review:
Epidemiological studies were included with data on modulatory properties of curcumin in cancer, through regulating the expression of cytokines, especially interferons. Letter to editor, case series, and case report studies, as well as epidemiological studies without data on modulatory properties of curcumin in cancer, were all omitted.

Phytochemical Research

Several studies have been performed on the beneficial effects of phytochemicals. Plant derived phytochemicals or secondary metabolites are active components in plants, which has always been an important source for plant growth and have also served a great role in clinical therapies by providing a wide variety of chemicals with often shows pharmaceutical activity. Phytochemicals have been used traditionally in herbal medicine due to their beneficial effects on health. Examples of commonly used phytochemicals includes flavonoids, steroidal saponins and organosulphur (Nilius and Appendino, 2013). Several of these compounds have biological and pharmacological functions and can be used to discover and design drugs. One of the medicinal used phytochemicals is polyphenols, which are found in foods such as cocoa powder, dark chocolate, vegetables, berries, non-berry fruits, beans, nuts and are amongst the most available antioxidants in the human diet. In recent years, a significant number of studies done to explore their pharmacological action have shown their positive health benefits (Afzal et al., 2015; Estrela et al., 2017; Annuzzi et al., 2014). Several studies have also shown that extracts from certain plants modulate the immune system response. The effects of immunomodulatory functions of several phytochemicals, such as polyphenols, flavonoids, and alkaloids, have also been demonstrated (Boland et al., 2014; Gandhi et al., 2018; Ferreira et al., 2015; Andreicut et al., 2018; H Farzaei et al., 2015). Unfortunately, immunological disorders are continually on the rise. This issue led to an effort to explore a particular group of molecules that are generally

termed immunomodulators. These molecules are capable of regulating the immune response in the immune system-mediated diseases. In this study, we concentrated on the immunomodulatory/anti-inflammatory role of curcumin and its action on interferons.

Curcumin

Curcumin or diferuloylmethane belongs to the ginger family and is an active ingredient found in turmeric and is widely found in the Indian subcontinent and Southeast Asia. Curcumin is an antioxidant and is widely known for its potent anti-inflammatory action (Vogel and Pelletier, 1815). India has the largest source of turmeric globally and it has since long been used as an Ayurvedic cure and as a flavouring agent (Priyadarsini, 2014). Based on its origins and growth conditions, turmeric derived from ground-dried root includes various amounts of volatile and non-volatile oils, carbohydrates, fats, minerals, proteins, curcuminoids and moisture. Curcuminoid is a linear diarylheptanoid with molecules such as curcumin or curcumin derivatives comprising of various chemical groups that have been established to improve the solubility of curcumin and make it appropriate for drug design. Among the curcuminoids family, curcumin has the highest amount (circa 70%) of curcuminoid, followed by demethoxycurcumin (20 - 27%) and bisdemethoxycurcumin (10 - 15%). Different types of curcuminoids have various strength, efficiency, and stability properties, but curcumin is not significantly superior to the other two compounds (Goel et al., 2008). In addition to curcuminoids, which are the most important active ingredient in turmeric, sesquiterpenes, diterpenes, and triterpenoids are other such active components that are also present (Abdel-Lateef et al., 2016). Numerous studies have revealed the safety and efficacy of curcumin in various diseases and pathological conditions (Ganjali et al., 2017; Panahi et al., 2014; Panahi et al., 2017; Parsamanesh et al., 2018; Salmaninejad et al., 2019; Kunnumakkara et al., 2017; Heidari et al., 2022; Bavarsad et al., 2019). Another important health benefit of curcumin that has been shown in many clinical studies is its anti-inflammatory effect (Peng et al., 2021). Besides the properties mentioned earlier, several studies have shown the immunomodulatory role of curcumin in various conditions.

Curcumin interacts with different immunomodulators, including immune system cells and molecular compounds produced during inflammation (Haftcheshmeh et al., 2019; Aggarwal et al., 2007; Pari et al., 2008). Although the immunomodulatory properties of curcumin have not yet been fully established, several researchers have described the antibacterial and antiviral function of curcumin, which makes it a natural immune-enhancer (Zhou et al., 2011; Ali et al.,

2017). On the other hand, some studies have displayed the suppressive properties of curcumin in response to an infectious agents, indicating that curcumin can also suppress immunity (Kunnumakkara et al., 2017; Boozari et al., 2019).

Curcumin and cancer

Cancer is one of the principal causes of mortality in developed countries (WH, 2003). Over recent years, an increase in early detection methods and treatment options have reduced cancer mortality to a significant amount. However, due to the emergence of drug resistance to various cancers, there is an increasing need for new and more efficient drugs (Barone et al., 2018). The development of tumor cells involves several signaling pathway dysfunctions, including overgrowth, cell death, and angiogenesis (Al-Ejeh et al., 2010; Udagawa and Wood, 2010). Previous studies have shown that disorder of various inflammatory pathways leads to cancer development. Chronic inflammation and persistent release of pro-inflammatory factors such as reactive oxygen species (ROS), cytokines, cyclooxygenase-2 (COX-2), transcription factors including NF-κB, protein kinases B (PKB), AP-1 could potentially stimulate the development and progression of various malignancies. Curcumin have shown to have anti-cancer properties resulting from its interaction with several immune mediators (Iranshahi et al., 2010; Mohammed et al., 2021; Afshari et al., 2021; Mohajeri et al., 2020; Giordano and Tommonaro). Curcuminoids could benefit cancers that involve inflammatory pathways by inhibiting NFκB and STAT-3 transcription factors and their downstream targets (Aggarwal et al., 2006). Nevertheless, curcuminoids also prevent the signaling of STAT-1 essential for anti-tumor response through interferon-gamma (IFNγ). Excessive activation of the NF-κB transcription factor is found in the tumors of the hematopoietic and lymphoid tissues, blood malignancies, myelodysplasia, and most solid tumors. Curcumin exerts its positive anti-cancer effects by inhibiting NFκB, which induces apoptosis in tumor cells. Furthermore, curcumin also inhibits the production of IFN-γ, which highlights on its potential anti-tumor effects. Also, continuous STAT3 activation causes the suppression in antitumor cytokines (such as IFN-α, -β, and –γ). (Tolomeo and Cascio, 2021; Wang et al., 2022; Wang et al., 2004).

Curcumin and signaling pathways

I- NF-KB signaling

NF-κB, as one of the principal pro-inflammatory transcription factors (TF) can modulate the up-regulation of several proteins such as cytokines IL1, IL-2, and IFNγ, that participates in

various cell inflammatory signaling pathways related to tumor development and progression (Sethi and Tergaonkar, 2009). The binding of NF-κB to DNA leads to the initiation of oncogenes' transcription that inhibits cell death and initiates cell growth and angiogenesis. Curcumin suppresses NF-κB activation by blocking the phosphorylation by inhibitory kappa B kinases (IKK) and blocking the nuclear translocation of the NF-κB p65 subunit. Activator Protein-1 (AP-1), associated with the pro-angiogenic, mitogenic and anti-apoptotic genes, is also suppressed by curcumin. Curcumin has been shown to have antitumor effects in various in vitro models, that is achieved by suppression of AP-1 and NF-B transcription factors (**Figure 2**) (Shanmugam et al., 2015). Additionally, specific protein kinases, such as IκB kinases, MAPKs, and ERK1/2, control the activity of NF-κB and AP-1 transcription factors; therefore, their modulation could potentially slow cancer progression. In addition, some studies have depicted the role of curcumin in inhibiting the protein kinases that is associated with an apoptotic function (Yao et al., 2015). Furthermore, curcumin exerts its anti-cancer effects by modulating cyclin D1 which is one of the proteins involved in the cell cycle. Curcumin can function as a transcriptional regulator. However, it has also been shown that an increase in cyclin D1 levels might leads to the initiation and promotion of tumors. Curcumin represses the production of cyclin D1 by inhibiting NF-κB (Bimonte et al., 2015). Besides modulating the immune network at the molecular level, curcumin also exerts its immunomodulatory properties by affecting cellular components such as MQ, DCs, and T and B cells (Momtazi-Borojeni et al., 2018; Ghasemi et al., 2019). Extensive researches done on this behalf have demonstrated the immunomodulatory mechanisms of curcumin (Chamani et al., 2022; Yuandani et al., 2021; Cohen et al., 2009; Salminen et al., 2011; Han et al., 2018).

As discussed above, curcumin regulates transcription factors, including NF-κB, by a variety of methods. One of these methods is inhibition of IKK-β activation (Cohen et al., 2009). In a study, curcumin consumption was noted for an individuals affected with head and neck cancer, and it was shown that consumption of curcumin contributed to a decrease in IKK-β activity in the saliva of these individuals and also reduced the up-regulation of cytokines including TNF-a, IL-8, and IFN-γ (**Figure 2**) (Kim et al., 2011). Another method of regulating NF-κB by curcumin is through IκBα (Han et al., 2018; Chen et al., 2019; Jobin et al., 1999). Curcumin treatment inhibits IkBa degradation, IkB serine phosphorylation, and IκB kinase (IKK) activity, thereby suppressing pro-inflammatory gene expression (Jobin et al., 1999). Furthermore, curcumin also trigger 5' AMP-activated protein kinase (AMPK) activation (Han et al., 2018). Various researchers have shown that curcumin inhibits NF-kB signaling after infection with the Influenza A virus (IAV) due to AMPK activation (Han et al., 2018). Moreover, curcumin

disrupts the NF-κB signaling pathway by acting on the p65 subunit (Xu and Liu, 2017). Infection with type A influenza virus resulted in a reduction of p65 subunit in the cytosol of MQs and a similar rise in the nucleus, where it produces an efficient complex with NF-kB, eventually increasing the expression of pro-inflammatory cytokines. Subsequently, curcumin also inhibits the nuclear translocation of NF-kB and p65, which reduces the expression of cytokine genes.

2. II- JAK/STAT Signaling

One of the crucial pathways to control inflammation in immune cells is the Janus kinase (JAK)-signal transducer and transcription (STAT) pathway activator. This pathway transmits the signal from type 1 and types 2 cytokine receptors in response to pro-inflammatory cytokines (O'Shea et al., 2013; Leonard and O'Shea, 1998). The four Janus kinases (JAK1-3 and TYK2), are related to the receptors described above along with the 7 STATs (STAT1-4, 5a, 5b, and 6) which are also included in this pathway (Leonard and O'Shea, 1998; O'Shea et al., 2013). These intracellular molecules mediate type I and type II interferon-induced signaling pathways (Schindler et al., 2007). JAK / STAT signaling controls the stimulation and development of various subtypes of T lymphocytes, involving T helper 1 Cell (, STAT1, STAT4, TYK2, JAK2,), T helper 2 Cell (STAT6, JAK1, JAK3) and T helper 17 Cell (STAT3), from naive CD4 + T cells, in the adaptive immune system (O'Shea et al., 2013; Leonard and O'Shea, 1998; Tamiya et al., 2011). It has been shown that curcumin inhibits the phosphorylation of JAK1 and 2 in microglia activated with gangliosides. In addition, curcumin also shows its effects through inhibition of STAT1 and 3 in IFN-γ, gangliosides, LPS-activated microglial cells or curcumin inhibited JAK / STAT signaling pathways. Curcumin has been shown to inhibit several pro-inflammatory mediators, such as nitric oxide synthase (NOS), COX-2, MCP-1 / CCL2, and intercellular adhesion molecule 1 (ICAM1) in the glial cells (Kim et al., 2003). By inhibiting STAT3 activation, curcumin stimulates tumor apoptosis and repress STAT1 phosphorylation through IFN-al without affecting STAT5 phosphorylation (Bharti et al., 2003). Concerning the antitumor activity of curcumin, its ability to inhibit certain innate immune responses and its action on Jak-STAT signal transduction is still debatable (Kim et al., 2003; Bharti et al., 2003; Jagetia and Aggarwal, 2007; Jeong et al., 2009; Blasius et al., 2006). Curcumin altered STAT1 activation in murine dendritic cells and inhibited indoleamine 2,3- dioxygenase (IDO)–mediated suppression of T-cell responses (Jeong et al., 2009). Also, curcumin administration to ascites carcinoma mice inhibited tumor-induced apoptosis in splenocytes and thymocytes (Jagetia and Aggarwal, 2007). In addition, curcumin also suppressed the immune effector cells

that promote immune-mediated tumour detection, including the proliferation of cytotoxic T lymphocytes by IL-2 and the expression of costimulatory molecules CD80 and CD86 (Paul and Sa, 2021; Kim et al., 2003).

Modulatory properties of curcumin on interferons in breast cancer

Breast cancer (BC) is one of the most common reasons for cancer mortality amongst female population globally (Akram et al., 2017). The incidence of breast cancer ranges from 27 per 100,000 in Middle Africa and East Asia to 92 per 100,000 in Northern America (DeSantis et al., 2015). Early diagnosis is the best way to improve mortality and morbidity due to breast cancer. Antiestrogens are one treatment modality for BC, and over 70% of BC individuals are positive for oestrogen receptors (ER). NF-κB plays a key part in the proliferation of BC cells. NF-κB regulates over 500 genes associated with various human diseases and cellular signaling pathways, causing tumors and inflammatory conditions. Several compounds can interact with NF-κB and it may be used in the management of various malignancies. Notably, curcumin has been shown to downregulate NF-κB, which in turn affects the BC cell proliferation and invasion (Kim et al., 2012; Liu et al., 2009). Furthermore, curcumin by up-regulation of retinoid-IFN-induced mortality 19 (GRIM-19) can increase the effects of β-interferon and retinoic acid on BC cells. It was noted that IFN-β/RA and GRIM-19 had significant anti-tumor effects in cell growth and embryonic development in several animal models and clinical studies (Mehrabian et al., 2007). Dysregulated expression of GRIM-19 has been detected in several cancers (Zhou et al., 2009; Alchanati et al., 2006). The treatment of BC with IFN-β/RA showed a decrease in sensitivity to the drug. However, whether combination therapy can overcome drug resistance and increase drug sensitivity in BC cells remains to be answered (Ren et al., 2017).

Modulatory effects of curcumin on interferons in lung cancer

Lung cancer is another leading cause of cancer death in the US and in other countries worldwide (Ferlay et al., 2015). Based on the tumor aggressiveness and stage, the 5-year survival in lung malignancies differs from 4–17% (Society, 2014). In recent years, considerable development has improved primary detection, monitoring, and new therapies. Studies demonstrated the action of curcumin and reported that curcumin downregulated NF-κB and inhibited JAK2 activity in a human lung cancer cell line (A549 cells) (Vadukoot et al., 2022). Furthermore, curcumin markedly downregulated protein levels of the JAK2/STAT3 pathway

(Sun et al., 2022; Hu et al., 2021; Zhang et al., 2013; Wu et al., 2015). Administration of curcumin (1500 mg/capsule for 14 days) via down-regulation of FOXP3 and up-regulation of interferon-γ (IFN-γ) converted Treg cells into Th1 cells in individuals with lung malignancies. Consequently, the number of Th1 cells increases, causing immune reactions against lung cancer cells (Zou et al., 2018; Ashrafizadeh et al., 2020).

Modulatory effects of curcumin on interferons in melanoma

Curcumin has been shown to induce apoptosis attributed as a result of down-regulation of proteins involved in the survival of human melanoma cells. Nevertheless, pre-treatment with curcumin blocked IFN-α– and IFN-γ–induced signal transduction in human melanoma cell lines. Pre-treatment of peripheral blood mononuclear cells from healthy donors with curcumin also blocked the ability of IL-2, IFN-α and IFN-γ to phosphorylate STAT proteins that are important for their anti-tumor response. Besides, in vitro researches have reported that curcumin modulated NK cells to produce IFN-γ in response to IL-12 and blocked the cytotoxicity of A375 human melanoma cells. Additionally, curcumin can inhibit cancers contributed by chronic inflammation, may also reduce the cellular reaction to immunotherapeutic cytokines that mediate cancer immunosurveillance (Kötting and Hofmann, 2021; Wang et al., 2020; Bill et al., 2009). Data indicated that curcumin might have a detrimental influence on immune cell response to clinically important cytokines. The antitumor actions of administered IFN-α in murine models of melanoma depended on the signal transduction of STAT1. Similarly, by promoting IL-2-induced cell cycle progression in T cells, its role in regulating normal immune function of STAT5 transcription factor also comes into play (Behbod et al., 2003; Fung et al., 2003; Yu et al., 2000). It also controls proliferation and cytolytic activity regulated by NK cells. The immunomodulatory effects of curcumin have not been completely deciphered because previous studies in murine models have not evaluated blood or tissue levels of curcumin. In vivo experiments were conducted to note sufficient curcumin concentrations required for inducing apoptosis in tumor cells. Until now, we have preliminary information about in vivo bioavailability and absorption of curcumin, for instance, the heat-mediated 12-fold increase in curcumin's aqueous solubility (Tabanelli and Brogi, 2021; Kurien et al., 2007). Similarly, in combination with an extract from black pepper (piperine), curcumin has been shown to increase the bioavailability of curcumin by 1000% in healthy human volunteers (Miljković; Shoba et al., 1998). This influence is mainly due to the capacity of piperine to suppress hepatic and intestinal glucuronidation which inhibits the metabolization of curcumin (Shoba et al., 1998). The present results suggest that careful

attention is needed to establish the immunomodulatory effects of curcumin to eliminate tumor cells and induce apoptosis.

Modulatory effects of curcumin on interferons in pancreatic cancer

Pancreatic cancer is ranked as the 7th highest cause of cancer mortality worldwide. Due to the lack of effective medications for pancreatic adenocarcinoma, this form of cancer prognosis is very poor. The genetic pathways behind pancreatic cancer mainly remain unknown at present. Understanding how signaling molecules function together to control the pathogenesis of pancreatic cancer can help develop novel treatments. However, it remains a significant obstacle worldwide to establish a successful treatment plan for pancreatic cancer (Yang et al., 2017). In combination with omega-3 fatty acids, curcumin have shown to increase the NK cell-induced apoptosis of pancreatic cancer cells, while curcumin alone could only inhibit interferon-γ production (Zhou et al., 2022; Fiala, 2015).

Modulatory properties of curcumin on interferons in colorectal cancer

Colorectal cancer (CRC) is the third leading reason of cancer death in the United States. Therefore, there is a major need for effective and non-toxic agents that could be utilized for managing CRC. Curcumin can act as a free radical scavenger to modify the gene expression of different stress proteins and genes involved in angiogenesis. In addition, Curcumin can also inhibit the action of many transcription factors (NF-κB and AP-1), inhibit the proliferation of cells and in turn the production of cytokines. Thus, the use of curcumin in chemoprevention and as a complementary treatment of CRC in future is much promising (Ierardi and Di Leo; Villegas et al., 2021; Park and Conteas, 2010).

Conclusion

The active ingredients in medicinal plants have long been the main source of managing various disorders, given their potential biological effects. Several of these natural ingredients have significant pharmacological activity that can be used to develop and design pharmaceutical agents. However, the discrepancies in immunomodulatory properties of herbal remedies have been highlighted, primarily due to limitations such as lack of standardization of active ingredients, qualitative and quantitative improvements in formulations, and lack of a comprehensive efficacy evaluation. The quest for new successful medicines capable of managing cancer diseases remains a priority for scientists. Herbal medicines have been applied

broadly in medicine and provide several active molecules for controlling several illnesses, including neurodegenerative, cardiovascular, inflammatory disorders and malignancies. Curcumin is one of the most promising bioactive herbal products for adjuvant therapy in managing certain cancers. As discussed in this review, curcumin demonstrates its anti-tumor capability by targeting various cell signaling pathways, comprising various growth factors, cytokines, transcription factors, and genes that modulate cell growth and death. **Figure 3** shows the molecular targets of curcumin. Moreover, some of the modulatory function of curcumin in cancers is mediated through interferons. Altogether, despite various advantages, further experiments and clinical studies in humans are still required to confirm the potential of curcumin as an important anti-tumor agent.

Abbreviation list

BC	Breast cancer
CRC	Colorectal cancer
TLR	Toll-like receptors
PRP	Pattern recognition receptors
PAMP	Pathogens-associated molecular patterns
LPS	lipopolysaccharide
MHC	Major Histocompatibility complex
IFN	Interferon
ROS	Reactive oxygen species
COX-2	Cyclooxygenase-2
PKB	Protein kinases B
AP-1	Activator Protein-1
AMPK	AMP-activated protein kinase
JAK	Janus kinase
STAT	Signal transducer and transcription
ER	Estrogen receptors

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