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A REVIEW ON MEDICINAL BENEFITS OF CURCUMIN ON CANCER

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ABSTRACT

Developing new ways to fight cancer that are more effective and have fewer side effects is still a challenge in science and medicine today. Curcumin, a natural polyphenol found in the food spice turmeric, has been shown to inhibit the survival and proliferation of cancer cells and trigger apoptosis without promoting side effects. However, due to its low solubility and bioavailability, curcumin has not been used in cancer treatment. Increasing understanding of cancer cell cycle dysregulation has spurred the introduction of phytochemicals in cancer therapy that can modulate signaling pathways that directly or indirectly regulate the cell cycle by altering cell cycle regulatory molecules. Most human malignancies are caused by chromosomal translocations or other genetic alterations that directly affect the activity of cancer cells, such as p53, as well as important cell cycle factors such as cyclin. In this context, the regulation of the cell cycle and its modulation by curcumin has attracted great attention in recent years.

Keywords: Cancer, Curcumin, Disease, Cell Metastasis.

I. INTRODUCTION

Cancer is second in life - threatening a disease and a major public health problem worldwide. In 2018, there were approximately 1.73 million new cancer cases and more than 609,000 deaths in the United States alone [1]. Research over the past 25 years has increased our understanding of the genetic makeup of cancer cells. It is now well known that cancer results from genetic mutations that lead to loss of growth control and cell differentiation, leading to cell proliferation, weakening, and eventually tumor formation [2] . There is growing evidence that people who rely more on fruits and vegetables in their diets have a higher risk of developing cancer [3]. The main groups of phytochemicals with disease-fighting properties are antioxidants, detoxification agents, and anti-inflammatory drugs. Such dietary phytochemicals include curcumin (diferuloylmethane), an important phenolic compound extracted from the rhizome of the Curcuma longa plant and used as a flavoring or yellow color in food or medicine [4, 5]. This phytochemical has long been known to have high antioxidant properties [6]. Because curcumin can inhibit cancer cells, cause apoptosis, inhibit angiogenesis, inhibit the expression of anti-apoptotic proteins, as well as inhibit the immune system of cancer cells - this can be without adjusting the value [4,7,8]. As cancer diagnosis is increasing and its treatment is expensive, it is important to find effective and efficient methods for patients in low-income and developed countries. Therefore, the motivation for this study is the use of cheap and affordable cancer treatments. To gain insight into the anti-cancer effects of curcumin, a systematic review of clinical studies on the use of curcumin and its effectiveness in the prevention and treatment of various types of cancer was conducted. Therefore, a systematic review of all published articles and other relevant literature on the use of curcumin in cancer treatment may provide a better understanding of many aspects of the effects of curcumin on cancer patients. During this review, only evidence from the best studies was selected to gather information and draw conclusions about the role and effectiveness of curcumin in all stages of treatment: Cancer. In medical literature, flavonoids are a broad subclass of the natural family of polyphenolic compounds and are the result of secondary metabolism of plants [9]. In recent years, the use and effectiveness of medical products in the treatment of various diseases has attracted great attention. He received good care. Many research projects have been carried out on extracting and analyzing the properties of herbal drugs in the treatment of various diseases such as cancer, and detailed information has been provided about the medicinal properties of these drugs. Among many medicinal products, curcumin is the main ingredient of the Curcuma longa plant. Its scientific name is "curcuma longa", its chemical name is "diferuloylmethane" and its chemical formula is C21 H20 O6 (as shown in Figure 1). 1) [11].

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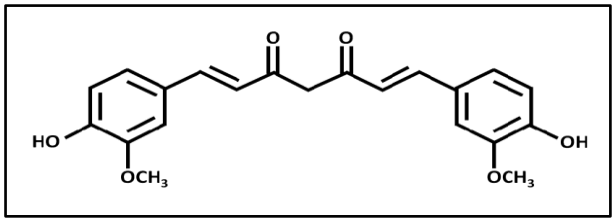

Fig 1. The chemical expansion of curcumin

Curcumin makes up 2% to 8% of the compounds in turmeric and is thought to be the main cause of turmeric's yellow/gold color and is also responsible for many of its other properties. 12, 13] a. Various studies have reported the antitumor activity of curcumin against breast cancer, lung cancer, head and neck squamous cell carcinoma, prostate cancer, and brain tumors. Curcumin and its derivatives have attracted great attention in the last two decades due to their biofunctional properties such as antibacterial, antifungal and antiviral. Curcumin exerts its anti-cancer effect through various mechanisms. Curcumin can inhibit the growth of many cancer cells by reducing the regulation of anti-apoptotic cells, activating caspases, and promoting tumor suppressors such as P53 [16–18].

Cancer escape cycle:

Cell growth and cell death are different cells, it is surprising how the two are connected and interconnected [19, 20]. There is a mechanistic overlap between the processes that direct growth and apoptosis. Instead, the two processes are coupled at different levels by various molecular actors responsible for cellular coordination. Importantly, the same players are often targeted by many growth-inducing mutations in concert with oncogenic mutations and mutations that inhibit the growth of time changes and apoptosis during cancer [21,22] . In other words, normal cells become malignant when cell proliferation is not under proper growth control. Of course, cancer cells also have other properties, such as inhibition of angiogenesis, metastasis and apoptosis. But ultimately, the basis of the disease is uncontrolled cell proliferation. Therefore, to understand cancer, we need to know about cell growth and control. The process of DNA replication and cell division can be described as a series of events that form the "cell division cycle". The mammalian cell cycle is divided into successive periods. G1, S, G2, and M phase transitions occur in response to growth or mitogenic stimulation (Figure 1). The stages of DNA synthesis (S phase) and mitosis (M phase) are preceded by different phases (G1, G2). Cell proliferation is tightly controlled by various interactions between molecules in a normal cell. A molecular system recognizes conditions that promote growth and sends signals to two groups of molecules that regulate cell division. Additionally, cells are equipped with signals that recognize conditions that are not necessary for growth. This pathway antagonizes the proliferative signaling pathway and can directly block cell division[23-25].

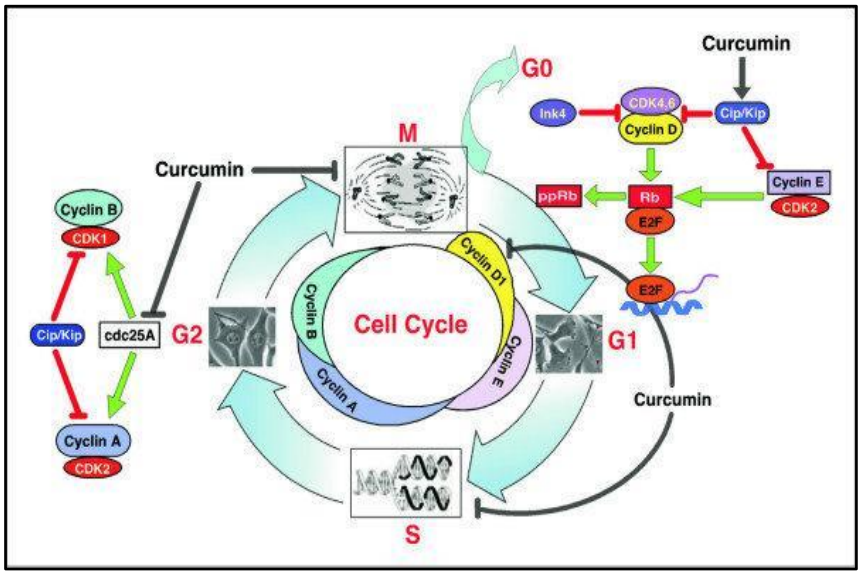

Fig 2. The cell division and its control.[26]

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II. ROLE OF CURCUMIN IN CANCER PREVENTION

Free radicals and chemical products produced by oxidative stress play an important role in the initial stages of cancer development. Thus, compounds with antioxidant effects help prevent tumor formation. Curcumin has properties that scavenge free radicals and therefore may play an important role in inhibiting the growth of cancer. Many cellular and preclinical studies have shown that curcumin can prevent DNA damage caused by oxidative factors (such as ionizing radiation) by inhibiting free radicals and reactive oxygen species [27]. Curcumin prevents cancer formation by inhibiting the formation of NF-kappaB [27,28]. Curcumin prevents tumor formation and growth by inhibiting and activating two enzymes (Phase 1 and Phase 2) [28].

Benefits of Curcumin on Cancer Cells:

While curcumin is used as a traditional medicine to treat many conditions, including inflammation, respiratory diseases and blood clots, its effects on cancer are rapid. development. The motivation to use curcumin stems not only from its therapeutic potential, but also from the fact that curcumin is more easily absorbed by patients without the side effects of many other medicinal products (such as nausea, vomiting, diarrhea). , hair loss [29] and more serious long-term conditions such as liver failure [30] . Various studies comparing breast cancer incidence and cancer rates in India and the West show that the risk of breast cancer is lower in India (Table 1) [31].

Table 1: Comparison of breast cancer incidence and mortality in India and the United States [31].

Types of cancer	USA		India	
Cancer	Cases	Deaths	Cases	Deaths
Lung	660	580	38	37
Breast	660	160	79	41
Prostate	690	130	20	9
Colon/rectum	530	220	30	18
Bladdar	202	43	15	11
Thyroid	55	5	12	3
Leukemia	100	70	19	17

III. WHY DOES CURCUMIN HAVE ANTI-CANCER PROPERTIES?

Generally speaking, there are different molecular markers involved in the pathogenesis and development of tumors of different origin. Curcumin can interact with various biochemical pathways of cancer cells and survive by directly or indirectly binding to different targets. Curcumin has been shown to interact with many targets, including transcription factors, growth factors, DNA, RNA, and many proteins involved in cell signaling pathways [32,33]. The chemical structure of curcumin has diverse properties that make it highly effective and has many synergistic properties for various molecular targets (Figure 2).

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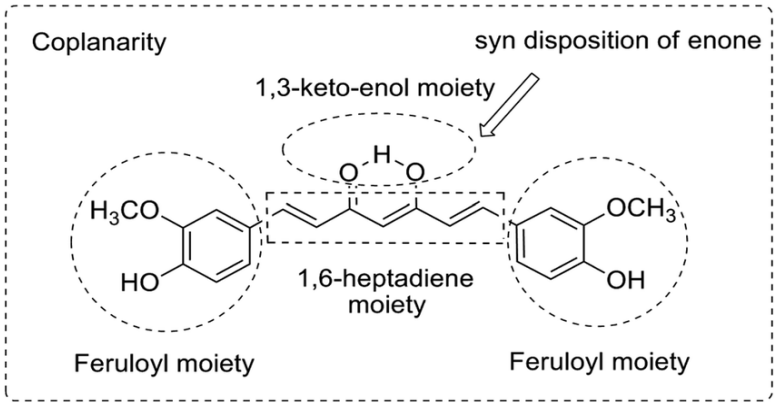

Fig 3. Structural features of curcumin involved in binding to protein targets.

Effects of Curcumin on Cancer Cell Metastasis, Angiogenesis and Inflammation:

Angiogenesis is the process of creating new blood vessels from existing vessels and depends on the amount of anti-angiogenic and angiogenic factor balance of the drug. However, in pathological situations such as tumor growth, this tight control is lost, leading to tumor metastasis. Many products produced by different cells play a role in the angiogenesis process. Hypoxia often occurs at the tumor site. To overcome hypoxia, tumor cells use hypoxia-inducible factor 1 (HIF-1) to control and regulate the expression of genes related to angiogenesis, cell cycle, metastasis, and immunity. HIF-1 was first recognized as a transcription factor associated with hypoxia-induced erythropoietin expression. This has been recognized as the main transcriptional regulator of these molecules [34,35]. Curcumin is a significant inhibitor of AP-1 activation, and recent studies have shown that curcumin is a direct inhibitor of HIF-1 transcription activity, leading to the transcription of many genes related to tumor angiogenesis [36,37]. Studies have also shown that curcumin reduces the expression of membrane molecules, including bacterial cell adhesion molecule-1, vascular cell adhesion molecule-1 and E-selectin, which are involved in the function of cell adhesion (Figure 3) [38].

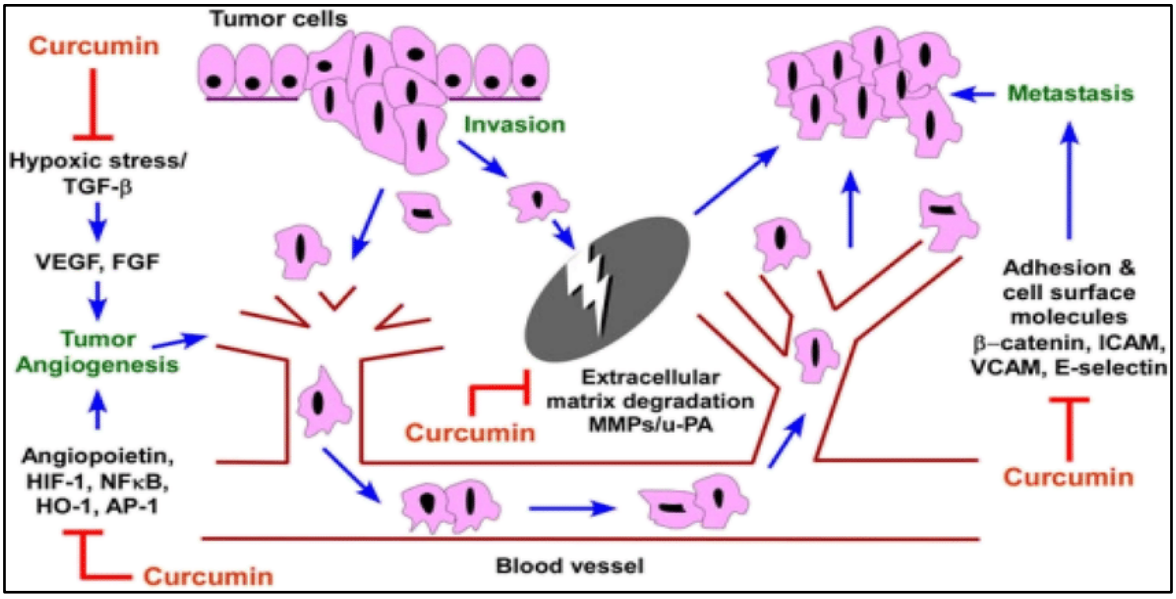

Fig. 4 Effect of curcumin on angiogenesis and metastasis of cancer cells [39].

The anti-inflammatory effects of curcumin have been confirmed by many studies. Since oxidative stress can cause inflammatory diseases, antioxidants can be used to prevent and treat inflammatory diseases [39, 40, 41, 42].

At the intersection of alternative and basic medicine:

Turmeric has been used in Ayurveda and traditional Chinese medicine for thousands of years. Today, curcumin (the yellow pigment in the spice turmeric) is still used as an alternative medicine in many parts of Asia to treat diseases such as stomach ache, bloating, jaundice, arthritis, sprains, pain and skin diseases. Expect Curcumin

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and turmeric products have been deemed safe by health authorities such as the U.S. Food and Drug Administration (FDA) and the Food and Agriculture Organization/World Health Organization (FAO/WHO). Curcumin has only entered clinical trials at the Phase I and II clinical trial level in the last 10-15 years. A phase III study of gemcitabine, curcumin, and celecoxib is about to enroll patients with gastric cancer at Sourasky Medical Center in Tel Aviv [43].

Fig 5. Turmeric plant with Rhizome

IV. CYCLIN-DEPENDENT PATHWAYS

Fuels of the Cell Cycle:

At least two types of cell cycle controls are known: protein phosphorylations that switch the cell from one phase to another; The team monitors checkpoints to complete important events and postpones them to the next stage if necessary. The first type of regulation involves the family of regulatory kinases [44–46]. Kinase activation usually requires binding to a second subunit that is transiently expressed in the appropriate phase of the cell cycle; The cyclic "cyclin" subunit binds its partner "cyclin-dependent kinase" (CDK), forming a specific substrate-specific active complex. Regulatory phosphorylation and dephosphorylation fine-tune the activity of CDK-cyclin complexes, resulting in precise changes in cell cycle phase. Completion of the G1 phase of the cell cycle is regulated by the sequential association and activation of three groups of cyclin-CDK complexes (Figure 5).

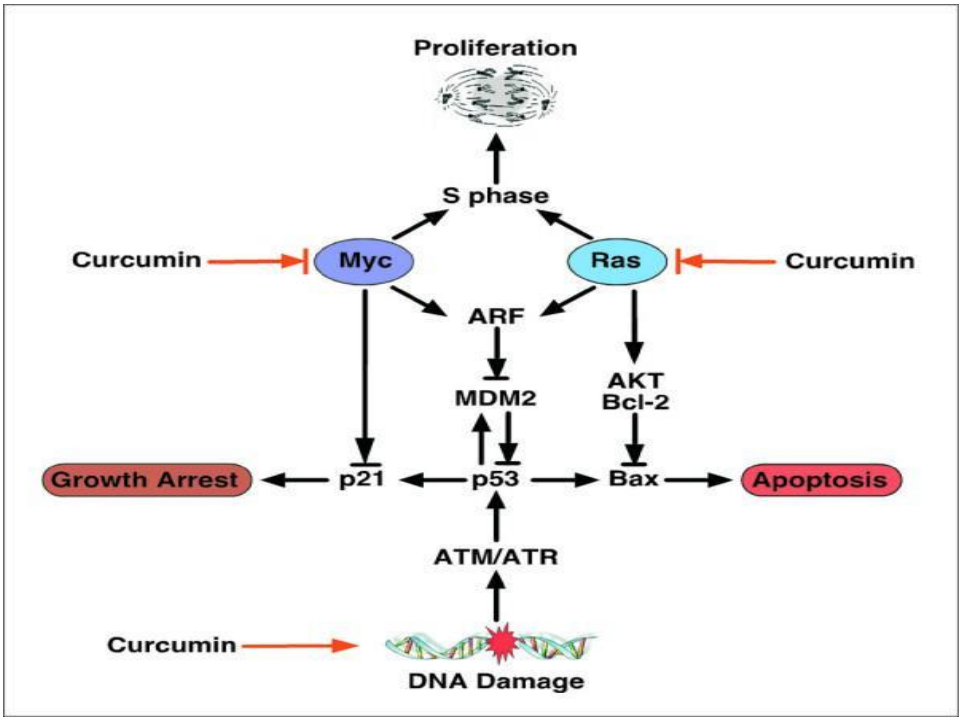

Fig 6. The ARF-p53 circuit in tumour development and therapy

D cyclins (D1, D2 and D3) and CDK4 or CDK6, cyclin E and CDK2, cyclin A and CDK2 [45,46]. In human cancer, genetic abnormalities in the regulatory circuits that control the G1 phase transition of the cell cycle occur frequently, and dysregulated overexpression of cyclin D1 is one of the most common alterations, possibly leading to the removal of the oncogene from cells. Cyclic law function [47]. In normal cells, cyclin D1 expression is tightly regulated by mitotic signals interacting with the Ras pathway [48] . Increased cyclin D1 abundance occurs early during tumorigenesis [49]. Overexpression of cyclin D1 in many types of cancer is caused by the induction of oncogenic signals rather than clonal somatic mutations or rearrangements in the cyclin D1 gene [50]. Tissue culture experiments show that cyclin D1 acts as an oncogene integrator and enhances the oncogenic transformation of other oncogenes (e.g. Ras, Src, E1A) [51, 52]. Targeted expression of cyclin D1 or cyclin E induces breast cancer [53,54] . Cyclin D and E-dependent kinases sequentially promote phosphorylation of the retinoblastoma gene susceptibility product (pRB), abolishing its ability to attack E2F elements and enabling the gene to enter S phase [44, 45]. Although the RB-1 gene was initially discovered for its role in rare childhood cancers, subsequent tumor studies have shown that the gene is mutated in many blood cancers [55]. In addition to direct mutations in the RB-1 gene, the transcriptional protein (pRB) inactivates pRB in many tumor cells through viral agents that bind to pRB or a change in the way the RB-1 gene works. Available mutational data indicate that almost all tumor cells have mutations or gene silencing mechanisms that result in suppression of pRB. This suggests that pRB is necessary to prevent entry into the cell cycle and prevent cancer. The cyclin-CDK-mediated pathway leading to the G1-S transition is called the "cyclin-dependent pathway". Regulation of G1-CDK activity is influenced by its association with inhibitory proteins called CDK inhibitors (CKi) [56]. So far, two families have been identified as structural and CDK targets of CKi: the Ink4 family and the Cip/Kip family [57].

V. CONCLUSION

Curcumin, the active ingredient of turmeric extract, has been used for many years as anti-inflammatory, antioxidant, anti-cancer and more. or in combination with The effectiveness and safety of combined use of other immune suppressants in cancer patients has been demonstrated in many human studies. Although there is much to learn about curcumin and its therapeutic properties, it has great potential in the treatment and prevention of cancer. Curcumin, a natural product, is not only non-toxic but also has many effects on various pathways involved in tumorigenesis.

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