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REVIEW ARTICLE

Curcumin and Cancer: Can It Supplement Chemotherapies for Cancers?

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Abstract: Despite advances in knowledge and information on the causes of cancers, prevention, the excellence of diagnostic systems, and the great achievements of oncology, the incidence of cancer still seems to be on the rise. The used chemical medications, in turn, have shown numerous side effects and cellular toxicity. That is why researchers have always been looking for anti-cancer drugs without adverse effects on the patient. Hence, herbal medicines have received special attention. Curcumin (diferuloylmethane) has been used as a spice in many countries around the world, including Iran, for centuries. Countless properties of this substance, which is obtained from the plant's root, such as anti-inflammatory, anti-mutagenic, anti-cancer, anti-fungal have been reported. This substance is able to affect cell signaling through multiple biochemical pathways, proliferation, differentiation, and cell death. The purpose of writing this review was to examine curcumin and its anti-cancer properties in a general view for its use in practical medicine.

Curcumin, with its epigenetic changes in the level of chromatin, is effective in regulating the expression of major and regulatory genes and can play a cancer-preventing role in the cell. Also, this substance and its compounds with inhibition activity of viral protein ACE-2 and Spike glycoprotein of SARS-CoV-2, and regulation of innate immune response have shown several roles in the fight against diseases.

To better understand the mechanism of action of turmeric metabolites with stimulant or inhibitory properties, it is necessary to do more research on the particular effects of Curcumin on various diseases, including cancer, effective dose and how to use it alone or in combination with other drugs.

Keywords: Antiviral activity; Cancer; Curcumin; Gene expression; Traditional medicine

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1. Introduction

Traditional medicine is the application of a combination of knowledge and skills in theories, believes, and local experiences, of various nations in providing health prevention, diagnosis, and treatment of diseases, be it physical or mental (1).

Plant-based medicines including herbs, plant substances, vegetative extracts, and active ingredients of plants are known as Herbal plants (1).

Well-known traditional medicine systems are Traditional Chinese Medicine (TCM) with a history of more than 3000 years (2), Ayurvedic medicine (Indian system of traditional medicine) , Unani systems, and in developing countries (3) like in Africa up to 90% of the population, 70% in India, and 40% in China are consumers of traditional medicine for all healthcare delivered (1). In the United States, throughout the year 2007, about 38% of adults and 12% of children used this type of medication (4, 5). It is estimated that the annual worldwide market for these products approaches US $60 billion, annually (6).

The study of specific native plants and their usage in traditional medicine (Ethnobotany) are considerable in both direct application as therapeutic herbs as well as basic materials for medicine industry (7). The origins of 61% of the 877 small-molecule drugs introduced worldwide between 1981 and 2002 are natural products. About 25% of the drugs pre-

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scribed worldwide are derived from plants (8). Also, 177 approved worldwide drugs for cancer therapy are reported from which more than 70% are based on natural or artificial products. Moreover, 90% of Eastern Mediterranean, South-East Asians, and Western Pacific populations are TCM consumers (figure 1) (9). The purpose of writing this review article is to investigate the effect of curcumin on chromatin, gene expression, and cancer prevention.

For writing this review, various databases such as PubMed, Google scholar, web of science, Scopus, and SID were considered for searching through keywords like Curcumin, cancer, traditional medicine, gene expression, and more. Articles whose full text was not available were excluded from the study. 62 articles, mostly from 2015, as well as reports from the World Health Organization (WHO), from various periods, were selected based on which had investigated and evaluated our desired subjects.

1.1. Curcumin and its ingredients

Turmeric is a product of Curcuma longa and belonging to the ginger family (10). It is derived from rhizomes of the plant known as "Indian saffron", dates back nearly 4000 years and had probably reached China by 700 AD, East Africa by 800 AD, and West Africa by 1200 AD. It is composed of more than 300 active components such as volatile oil which contain turmerone, one of the main components of the plant root. Its components can be divided into 2 main classes 1) Curcuminoids and 2) non-Curcuminoids (8). Diferuloylmethane, Natural yellow, Turmeric yellow, Curcuma, Indian saffron, Halad, Merita Earth, Terra Merita, and Yellow Ginger, are other synonyms of Curcumin (11).

Chemical and physical properties of Curcumin are summarized in Table1. Curcumin is not approved to have therapeutic indications and therefore is not considered as a drug, yet, but rather is known as an herbal and dietary supplement and is called a PAINS (pan-assay interference compounds) or IMPS (invalid metabolic panaceas) (12, 13).

Pleiotropic properties and multiple biological activities of curcumin are known (14) as Anti-inflammatory (15), Anti-bacterial (16), Antimutagenic, Anti-fungal, Anti-cancer, Antioxidant, anti-atherosclerotic, Anti-angiogenic, Anti-epileptic, Antiviral, Hepatoprotective, Wound-healing, and Antidiabetic (17, 18). So far, 15,062 articles about curcumin and 5,423 papers about turmeric medical effects are published. 226 of the papers are reported as worldwide clinical trials, 103 are completed experimental research, and 430 have remained as conditional investigations (clinicaltrials.gov). Also, according to the Iranian Registry of Clinical Trials (https://www.irct.ir), 173 clinical trials have been registered in Iran (19).

1.2. Metabolism/ Pharmacokinetics of Curcumin

Curcumin has poor absorption into the gastrointestinal tract. Oral administration of a single dose of 2g of curcumin in rats has resulted in a plasma concentration of fewer than 5 μg/mL of the substance (20). Following entry to the gastrointestinal tract, curcumin is quickly metabolized and forms Curcumin glucuronide, Curcumin sulfate, Tetrahydrocurcumin, Hexahydrocurcumin, and Exahydrocurcuminol (21). Also, curcumin would sustain sever latter metabolism in the liver resulting in major metabolites as glucuronides of tetrahydrocurcumin and hexahydrocurcumin, with dihydroferulic acid and traces of ferulic acid, tetrahydrocurcumin, preserve anti-inflammatory, and antioxidant attributes (22, 23).

Holder et al. (1978) reported some excreted doses of (3) H-curcumin in the bile of cannulated rats and showed its major metabolites were glucuronides of tetrahydrocurcumin and hexahydrocurcumin, while the minor metabolite was dihydroferulic acid together with traces of ferulic acid (24). Wahlstrom B., and Blennow G, (1978) showed that when curcumin is given to rats orally at a dose of 1 g / kg, up to 75% is excreted in the feces, while small amounts of curcumin appear in the urine. Measurement of blood plasma levels and biliary excretion showed that curcumin was poorly absorbed from the gut while negligible amount appeared in urine (25).

Anticancer effects of curcumin have been studied in different cancers like Gastrointestinal, Genitourinary, Brain, Breast, Gynecologic, thoracic, Melanoma, Bone, and Hematological cancer (26, 27).

Main characteristics of curcumin that are involved in its anticancer property are Anti-inflammatory, Anti-oxidative, Anti-proliferative, Anti-angiogenic, and Apoptosis inducing (28). Moreover, curcumin modulates different signaling pathways from which the following are introduced; PI3K/AKT/mTOR pathway, MAPK signaling pathway, p53 signaling pathway, Wnt/β-catenin pathway, NF-KB pathway (29, 30) HIF-1 pathway, Activating protein-1 pathway, Wilms' tumor 1 pathway, Nrf2 pathway, EGFR pathway, STAT3 pathway (31), and Notch 1 pathway (32, 33). Curcumin suppresses growth, angiogenesis, invasion, and metastasis of cancers through up/downregulation of multiple molecular targets (34). More recently, it is shown that curcumin can modulate the targets that are inhibited by FDA-approved drugs for the treatment of cancer (35-37).

1.3. Gene expression changes and epigenetic alterations

High-throughput studies have revealed that curcumin affects the expression of divers' protein-coding genes and microRNAs. Ramachandran et al. (2005) studied gene expression changes in MCF-7(38). Chiang et al. (2015) incubated NCI-H460 cells (human non-small-cell lung cancer cell line) with

and without curcumin (2 μM) for 24 h, and compared gene expression differences between treated and untreated cells using high-density microarray (39). The outcome demonstrated that 170 genes were remarkably upregulated, and 577 genes were seriously downregulated in curcumin-treated cells. The most of DEGs (differentially expressed genes) were associated with DNA damage, cell cycle, and survival incubated NCI-H460 cells (40).

1.4. Histone deacetylation

Curcumin functions as an HDAC2 activator in heart failure (41), while it has been reported that the substance down-regulates HDAC1, 2, 3, 4, 5, 6, 8 and 11 in various cancer cell lines and mice (42), and inhibits HDAC activity(43).

1.5. Histone acetylation

Curcumin is a specific inhibitor of the p300/CBP family with no effects on other HATs like PCAF/GCN5 (44). It acts as CBP/HAT inhibitor, enhances p300 degradation, inhibits histone hyper acetylation, down-regulates H3 and H4 activation, acetylates p53(45), suppress GCN5 linked with hypo-acetylation of histone H3(42), direct inhibition of p300, HAT activity suppression (46), hypo acetylation of p65 isoform of NF-kB(47).

1.6. DNA methylation

Methylation of DNA is a type of transmissible change in the DNA that does not alter coding nucleotide sequence; however, it can directly suppresses the expression of a gene. It has been observed that hypo-methylating activity of curcumin depends on the density of methylation owing to selective demethylation of partially methylated CpG regions other than fully-methylated genomic areas (42, 48). Covalently obstruction of the catalytic thiolate of DNA methyl transferase I, impedes DNMT3B (49), suppresses methyl transferase M.SssI at an IC50 of 30 nM, and provokes global genomic DNA hypo-methylation (50, 51). Curcumin exhibits reactivation of silenced tumor suppressive genes by inducing demethylation of promoters of RARb2 in human cervical cancer cell lines and p15INK4B in acute myeloid leukemia (52) (53), leading to a remarkable tumor suppression induced the reversal of methylation of Nrf2 promoter in prostate cancer cells (54).

Hassan et al. (2015) used DNA pyrosequencing and global DNA methylation analysis and reported that both curcumin and its structural analog dimethoxycurcumin (DMC) did not reveal any significant hypo-methylation activity even at very high concentrations (55). Surprisingly, they considered the elevated expression of promoter-methylated genes by DMC without converting DNA methylation (56).

1.7. miRNA expression

miRNAs regulate the gene expression at the level of mRNA degradation and translation. miRNAs may suppress cancer or exert oncogenic effects (57). A classification of specific miRNAs expression levels which is significantly changed by curcumin administration is reported (57). Curcumin is used as an adjuvant and showed that it may have synergistic effects in combination with chemotherapy or radiotherapy in eliminating tumor cells (table2) (58, 59). Both turmeric and curcumin are considered to be generally safe and have not been linked to liver injury in any consistent way (60). Studies of its use in various clinical conditions have found low rates of transient and asymptomatic serum enzyme elevations during therapy but without instances of clinically apparent acute liver injury (61). Indeed, turmeric has been evaluated as therapy of acute and chronic liver injury, although its efficacy and safety in this situation have not been verified (62).

1.8. Antiviral activity of curcumin

Recent articles report of Curcumin inhibition activity of viral entry into cells, suppression of viral replication, stimulation of interferons (IFNs), and inhibition of viral protein expression (63). Curcumin has an affinity towards ACE-2 and Spike glycoprotein of SARS-CoV-2 (64).

The results of recent research show that VCG Plus, a curcumin based substance, can act on 88 hub targets which are closely connected and associated with immune and inflammatory responses (65). VCG Plus showed that it has the potential to regulate innate immune response by acting on NOD-like and Toll-like signaling pathways to promote interferon's production, activate and balance T-cells, and regulates the inflammatory response through inhibiting PI3K/AKT, NF-KB and MAPK signaling pathways (65).

2. Conclusion

Examination of Curcumin and its compounds, its intervention in various signaling pathways and control of cells activities, and thus its effects on the pathogenesis of diseases, especially cancer, reveals the numerous benefits of this substance. Therefore, more research on Curcumin, this golden substance, is recommended in the treatment of diseases in animal models and/or in human populations with high consumption of turmeric.

3. Appendix

3.1. Acknowledgements

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3.2. Author contribution

All authors have the same contribution.

3.3. Funding/Support

None.

3.4. Conflict of interest

The authors declare that they have no competing interests.

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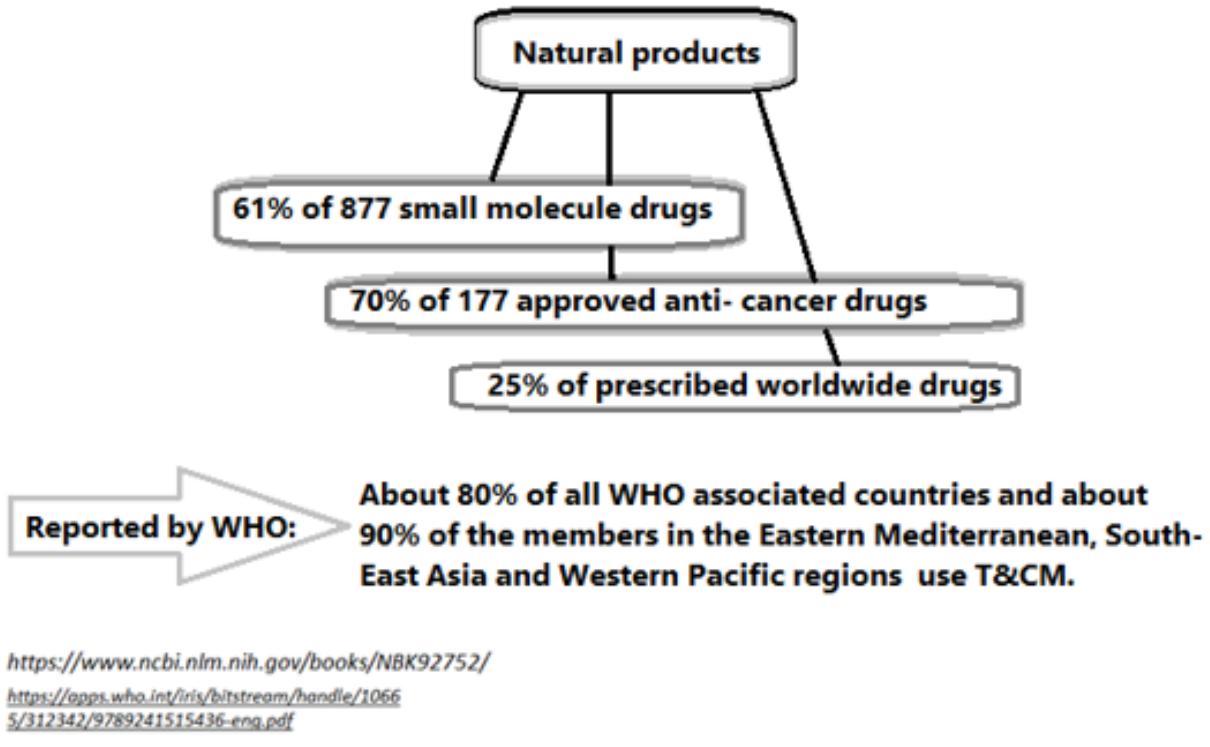

Figure 1: A Brief history of traditional medicine and herbal remedies. T&CM: Traditional Chinese medicine. Illustrated by the authors according to Newman DJ, Cragg GM. 2012 (8).

Table 1: Chemical and physical properties of Curcumin (66, 67)

Molecular Weight	368.4 g/mol
Physical Description	Solid, Orange-yellow crystalline powder
Melting Point	183.0 °C
Solubility	Insoluble in cold water Very soluble in ethanol, acetic acid
Fluorescence	Slightly fluorescent

Table 2: A number of recent studies on the effectiveness of curcumin in the treatment of cancers (59)

Type of Cancer	Treatment	Participants	Findings
Advanced or metastatic breast cancer	Curcumin (500 mg/day) and escalated until a dose-limiting toxicity + docetaxel (100 mg/m^2) for 7 days every 3 weeks	14 patients	Improves biological and Clinical responses
Pancreatic cancer	Curcumin (8000 mg/day) + gemcitabine (1000 mg/m^2) weekly	17 patients	Time to tumor progression was 1-12 months and overall survival was 1-24 months
Chronic myeloid leukemia	Imatinib (400 mg twice a day for 6 weeks) Group B [Turmeric powder (5 g three times/day) + imatinib (400 mg twice a day)] for 6 weeks	50 patients	The suppressive effect of nitric oxide levels was noted at Group B
Pancreatic cancer	Curcumin (1000 mg/day) + gemcitabine (1000 mg/m^2 on day 1 and 8) and 60 mg/m^2 of S-1 orally for 14 consecutive days every 3 weeks	21 patients	Median survival time after initiation of curcumin was 161 days and 1-year survival rate was 19%
Colorectal liver metastases	5 M curcumin + 2 M oxaliplatin + 5 M 5-FU	12 patients	Curcumin enhanced the FOLFOX-based chemotherapy
Pancreatic cancer	Curcumin (2000 mg/day) continuously (4 capsules, each of 500 mg, every day)	44 patients (13 locally advanced and 31)	Median progression-free survival and overall survival were 8.4 and 10.2