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Review Article

Ameliorating Effects of Curcumin on Testicular Cancer

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In the young men's population, testicular cancer (TC) is characterized as one of the main causes of morbidity and mortality around the world. This cancer is mainly divided into germ cell and nongerm cell types and manifests different signs and symptoms, like bone pain, nausea, lower back pain, and anorexia. Also, TC is associated with serious conditions, such as urogenital disorders, infertility, cardiovascular diseases, and solid tumors. Unfortunately, common remedies for TC, including chemotherapy and surgery, have not provided a promising outlook due to their adverse effects on life quality. Ergo, finding a new therapeutic candidate with high effectiveness and low detrimental impacts is indispensable. Newly, herbal remedies have attracted much interest because of their potential to improve diverse diseases, like cancer. In this context, increasing evidence indicated that curcumin, as a polyphenol compound originating from the plant *Curcuma longa*, has beneficial effects for treating TC. Hence, in this narrative review, we aimed to review documents showing the therapeutic potential of this herbal candidate against TC.

1. Introduction

Testicular cancer (TC) is known as the most common malignancy, with increasing prevalence and high mortality and morbidity in young males throughout the world [1, 2]. Yearly, 10,000 deaths and 50,000 new diagnostic cases arising from TC are reported globally [3]. Based on pathological features, TC is divided into germ cells (with high prevalence) and nongerm cell tumors [4]. The tumors related to germ cells can be divided into seminoma, which is more common in germ cell-related tumors, and nonseminoma types [4]. Nongerm cell testicular tumors include 5%–10% of all testicular neoplasms [5]. The members of this group comprise sex gonadal stromal tumors, commonly derived from Sertoli or Leydig cells, mixed tumors, and tumors of hematopoietic or mesenchymal origin. Furthermore, multiple miscellaneous lesions, secondary testicular tumors, and tumor-like conditions can be considered nongerm cell tumors [6]. TC can manifest several signs and symptoms, such as bone pain, gastrointestinal hemorrhage, nausea, lower back pain, swelling in the lower extremities, weight loss, malaise, and anorexia [7]. Moreover, TC may be associated with serious conditions, such as urogenital disorders, infertility, cardiovascular diseases, leukemia, solid tumors, and thromboembolic conditions [8–12]. The standard curative approach for TC in the metastasis stage is primary surgical techniques, orchiectomy, along with three or four cycles of chemotherapeutic agents (cisplatin, etoposide, and bleomycin) [13]. Despite the high effectiveness of this therapeutic way, its detrimental effects on the quality of life have been recorded [14, 15]. Besides the

adverse effects of chemotherapy on the male reproductive system, unfavorable behavioral influences, like cognitive disorders, fatigue, and increased levels of depression and anxiety, have also been reported [16]. Ergo, replacing an effective and low side-effect method with chemotherapy and surgery approaches seems critical. Recently, herbal therapies have been appreciated in different communities in light of their beneficial effects on improving various disorders, such as cancer, infertility, cardiovascular diseases, diabetes, neurological ailments, etc. [17–21]. One of these proposed therapeutic candidates for TC is curcumin, a polyphenol compound obtained from *Curcuma longa*, which is used as a colorant, flavoring ingredient, and cooking spice [22–24]. Curcumin has been demonstrated to have antineoplastic functions in many malignancies by some mechanisms, for instance, suppressing cell proliferation, inflammation, invasion, angiogenesis, and metastasis of tumor cells, stimulating apoptosis, and sensitizing cancer cells to cancer therapies [25–29]. Hereby, in this narrative review, we aimed to review evidence indicating the therapeutic capacity of curcumin for treating this cancer.

2. TC and Its Pathogenic Mechanisms

Presently, the pathogenesis of TC has remained ambiguous yet. However, it is stated that the most critical risk factor for TC is undescended testis or cryptorchidism. At the beginning of the 19th century, the link between germ cell-associated tumors and maldescensus testis was recommended. It is believed that maldescensus testis can increase the risk of TC by two to four-fold [30]. Also, infertility can significantly predispose the male sex to TC. It is reported that TC patients have weaker semen quality and fewer children compared with normal subjects [31–33]. In addition, some maternal risk factors, such as increased estrogen levels, old age during pregnancy, and smoking, may have a pivotal role in TC pathogenesis [30, 34]. Regarding testicular germ cell cancers (TGCC), whose cytogenetic hallmark is a disturbance in the short arm of chromosome 12, it is thought that these tumors may be initiated at early embryogenesis and be a subgroup of testicular dysgenesis syndrome [35, 36]. According to a hypothesis supported by histological investigations, dysgenetic properties, like hyaline bodies and immature Sertoli cells with undifferentiated tubules, are mostly observed in TC [37–40]. These defects in testis development can reflect the suppression of differentiation of some early primordial germ cells/gonocytes; thus, these germ cells maintain their early embryonic indices [41–43]. Increasingly, documents have declared that TC is associated with variations in involved genes in steroidogenic enzymes and the hypothalamic–pituitary–testicular axis [44]. Therefore, variations in genes involved in hormone metabolism may be related to the hormonal status observed in TC [44]. Also, the upregulation of the expression of certain genes and gene expression regulators occurs in this cancer, for example, *p53*, *CACNA1F*, and *VEGFR2* [45–47]. Additionally, miR-372 and miR-373, as noncoding RNAs regulating gene expression posttranscriptionally, are upregulated in TGCC [48, 49]. These miRNAs imitate the influences of mutated p53, leading to cancer progression [50, 51]. These noncoding RNAs do not suppress p53 function by a direct route, and in fact, they target the large tumor suppressor homolog 2 gene directly [51]. However, the gene expression of *CMTM3* is mostly downregulated in testicular neoplasia through methylation of promotor at the Sp1/Sp3-responsive region [52]. This chemokine-like factor gene is located on chromosome 16q22, and its highest expression is in the testis [53]. Another point is that the increased expression of some chemokines, like CCL-5, CXCL-10, and CXCL-13, and pro-inflammatory factors, such as IL-1ß, tumor necrosis factor (TNF)-α, and IL-6, have been highlighted in TC (Figure 1); however, their exact pathogenic processes in TC have not fully illustrated yet [54].

3. Curcumin and Testis Cancer

Curcumin is described as an active polyphenol component in dietary spice (turmeric) and natural herbal therapy [55]. This polyphenol is nontoxic and has several biological and pharmacological influences, such as antitumor, antioxidative, anti-inflammatory, antimicrobial, and antiviral effects [55–58]. Several published papers have addressed the anticancer potential of curcumin in many cancers, e.g., breast, gastric, prostate, ovarian, pancreatic, colorectal, and cervical tumors [58]. Curcumin targets cancer cells through various mechanisms; for example, it inhibits angiogenesis, epithelial-mesenchymal transition, invasion, and metastasis of cancer through regulation of the expression of noncoding RNA related to cancer [59–62]. Other mechanisms by which curcumin affects tumoral disorders include suppression of different cell signaling proteins, like nuclear factor-kappa B (NF-κB), cyclooxygenase-2, activator protein 1, cyclin D1, matrix metalloproteinases, epidermal growth factor receptor, β-catenin, Akt, and also TNF [63]. With regard to TC, some evidence also expressed the possible therapeutic potential of curcumin (Table 1). In this direction, it has been declared that this herbal compound can trigger the apoptosis process in TC by elevating caspase-9, caspase-8, and caspase-3 activities and cytoplasmic Cyt-c and Bax levels and decreasing the Bcl-2 level [64]. Similar to these results, an investigation demonstrated synergistic effects of curcumin with bleomycin, the most common anticancer agent for treating TC, through reduction of cell viability and induction of caspase-dependent apoptotic signaling pathways, accompanied by a decreased Bcl-2 expression and increased Bax and Cyt-c levels in NTera-2 cell lines [65]. Interestingly, Cort et al. [23] demonstrated a positive role of curcumin in the improvement of the antioxidant defense system by reducing protein carbonylation (protein oxidation) and lipid hydroperoxide and promoting total antioxidant capacity in TC cells. However, in this work, the levels of glutathione (GSH), an antioxidant agent, in the NCCIT cells were significantly decreased [23]. According to some evidence, reduced GSH levels resulting from curcumin therapy in some cancer cells can be due to reactive oxygen species-independent factors [66]. In another effort by Zhou et al. [67], it was revealed that curcumin fights against TC through the apoptosis induction via the caspase-dependent apoptotic pathway, reduction of extracellular-regulated kinase (ERK) and protein kinase B (Akt) phosphorylation, transcription

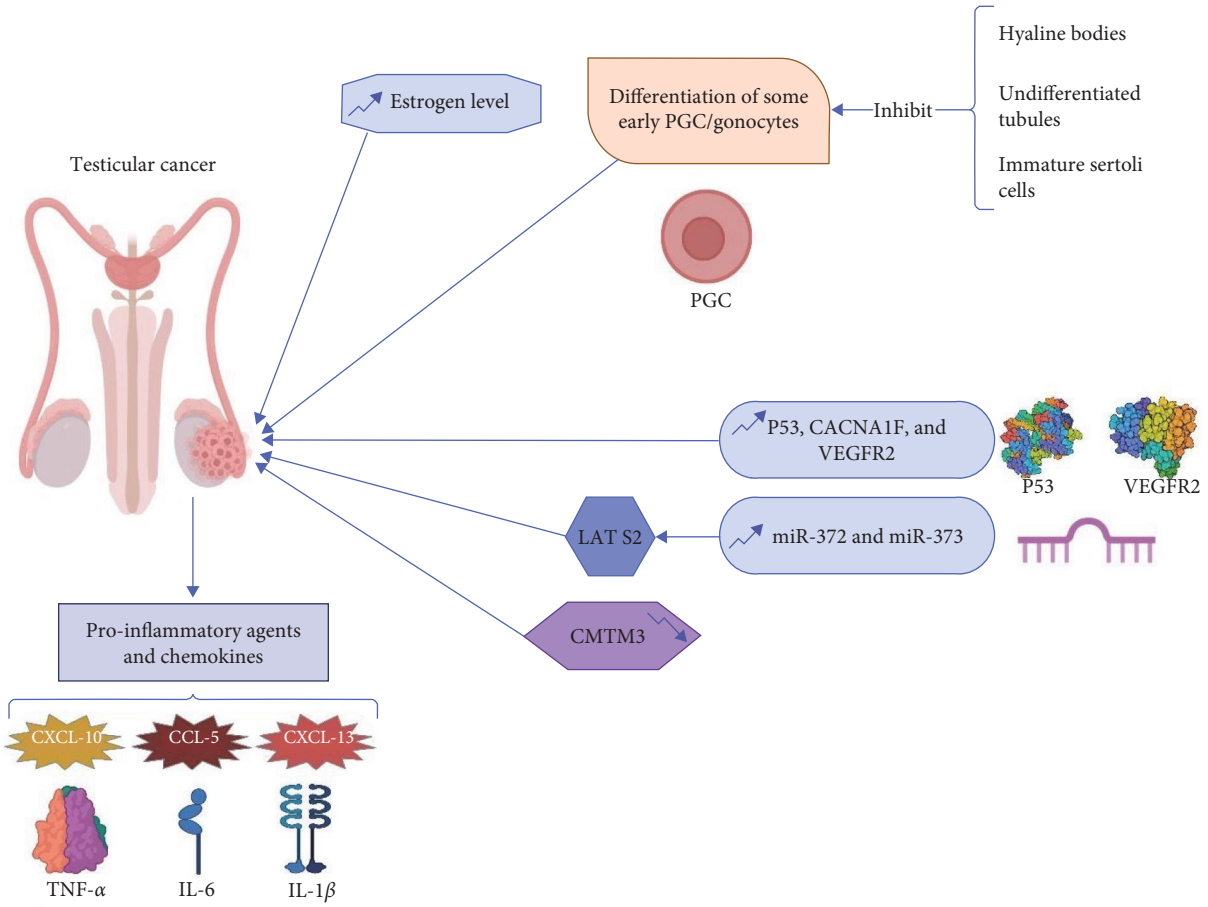

Figure 1: Some pathogenic agents are involved in testicular cancer incidence and progression. CACNA1F, calcium voltage-gated channel subunit alpha1 F; VEGFR2, vascular endothelial growth factor-2; miR-372, microRNA 372; miR-373, microRNA 373; CMTM3, CKLF-like MARVEL transmembrane domain containing 3; CCL-5, C-C chemokine ligand-5; CXCL-10, C-X-C motif chemokine ligand-10; CXCL-13, C-X-C motif chemokine ligand-13; IL-1β; interleukin-1β; TNF-α, tumor necrosis factor-α; IL-6, Interleukin-6; PGC, primordial germ cell; LATS2, large tumor suppressor homolog 2.

Table 1: List of studies in which the effect of curcumin on testicular cancer has been investigated.

Ref.	Cell line	Key findings	Curcumin dose
[69]	NTera-2	Inducing apoptosis, repressing cell proliferation, and decreasing AP-2γ expression	5, 10, and 15 μmol/L
[65]	NCCIT	Inducing apoptosis by increasing caspase-3, caspase-8, and caspase-9 functions and cytoplasmic Cyt-c and Bax levels and reducing Bcl-2 level	5 μM
[65]	NTera-2 and NCCIT	Attenuating GSH and lipid hydroperoxide levels and protein carbonylation in NCCIT cells and potentiating total antioxidant capacity in NTera-2 cells	5 and 20 μM
[66]	NTera-2	Reducing cell viability, elevating caspase-3, -8, and -9, cytoplasmic cytochrome c, and Bax levels, and diminishing Bcl-2 level	20 μM

factor AP-2γ expression, and suppression of ErbB2 expression, therefore it can inhibit malignant testicular germ cell proliferation and decreases cancer cell viability, and colony formation *in vitro* (Figure 2). AP-2γ, as a subclass of the AP transcription factor family, has a crucial role in the differentiation and development of germ cells and trophoblast, and recent results accentuated its role in self-renewal and viability of immature germ cells [68, 69]. AP-2 is a key trigger for the ErbB2 gene, whose loss function in cancer cell results in apoptosis stimulation and cell growth repression [67, 70]. Taken together, the present documents emphasize that this phenol can combat TC mainly by triggering apoptotic and antioxidant pathways. One of the substantial questions regarding curcumin therapy in malignancies, like TC, is how this polyphenol targets cancer cells without affecting normal cells. It seems that curcumin faces tumor cells and normal cells selectively. Results obtained from absorption and spectrofluorimetry techniques indicated that the cellular uptake of this natural compound is

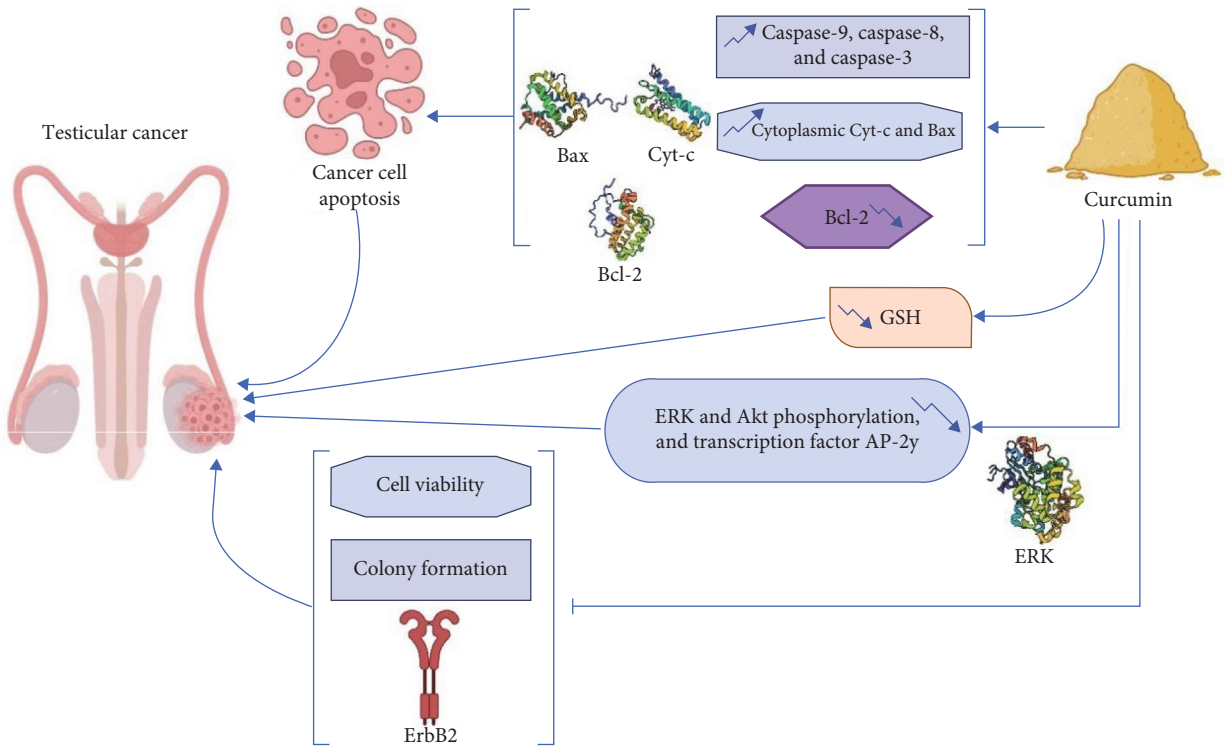

Figure 2: Curcumin, as a herbal candidate, can target testicular cancer cells through diverse mechanisms, like apoptosis induction, antioxidant system capacity promotion, and inhibition of cell viability and colony formation. ERK, extracellular-regulated kinase; AP-2γ, activator protein-2γ; Cyt-c, cytochrome-c; Bax, Bcl-2-associated X; Bcl-2; B-cell lymphoma-2; GSH, glutathione.

higher in cancer cells than in healthy cells [71]. Also, decreased GSH levels in tumor cells enhance the sensitivity of malignant cells to curcumin. Another effective factor in the targeted function of curcumin is related to its action on inflammatory agents. Curcumin represses cancer cell proliferation and viability by suppressing NF-κB, which is not expressed in normal cells by this herbal product [72]. However, more reports are needed to approve its exact effects and mechanisms on TC and normal cells *in vivo* and *in vitro*.

4. Conclusion

In the population of young men, TC is one of the main responsible of morbidity and mortality globally, and despite multiple efforts of researchers, it has not been proposed a functional treatment with high effectiveness and low side effects yet. Recently, a natural herbal remedy by the mediation of curcumin extracted from the plant *C. longa* has gained much consideration in the treatment of many cancers like TC. Some documents stated that curcumin targets TC cells through different mechanisms, like increasing caspase-9, caspase-8, and caspase-3 functions, and cytoplasmic Cyt-c and Bax levels, reducing Bcl-2 levels, ERK and Akt phosphorylation, GSH and lipid hydroperoxide levels, protein carbonylation, and transcription factor AP-2γ expression and inhibiting ErbB2 expression, cancer cell viability, and colony formation. However, more *in vivo* and *in vitro* researches are required to support these statements.

Data Availability

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Disclosure

This is a review article that summarizes past studies and the references used in the text. Figures were designed by the web-based software BioRender.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Reza Arefnezhad, Pouya Goleij, and Negar Heydari contributed to the acquisition, analysis, and interpretation of data for the work. Fatemeh Rezaei-Tazangi and Hossein Motedayyen contributed to the write-up of the review article.

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