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Original Article

Curcumin (Turmeric): A Carcinogenic, Miscarriage and Cirrhosis Causing Agent

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ABSTRACT

Background: Curcumin, a compound derived from the turmeric plant (Curcuma longa), has been historically used in Asian cuisine and traditional medicine. It is known for its anti-inflammatory and antioxidant properties and is believed to have therapeutic potential in various inflammatory and oxidative conditions. However, concerns have emerged regarding its safety at higher doses, particularly its potential carcinogenic, reproductive, and hepatotoxic effects.

Objective: The objective of this review was to evaluate the potential adverse effects of curcumin, focusing on its carcinogenic, reproductive, and hepatotoxic properties, as well as general side effects observed at different dosages.

Methods: A comprehensive search was conducted using electronic databases such as PubMed, Scopus, and Web of Science to identify peer-reviewed articles published up to the date of this review. The search terms included "curcumin," "turmeric," "carcinogenic," "miscarriage," "hepatotoxicity," and related keywords. Studies were included if they investigated the biological effects of curcumin in vitro, in vivo, and in clinical settings, specifically addressing its adverse effects. Data were extracted on study design, sample size, dosage, duration of curcumin administration, observed adverse effects, and conclusions. Quality assessment of the studies was performed using standardized tools appropriate for different study designs. The data were synthesized qualitatively and presented in a narrative format, with tables summarizing key characteristics and results.

Results: The review included numerous studies that reported adverse effects of curcumin at higher doses. Curcumin was found to cause DNA damage and chromosomal aberrations at doses of 10 µg/mL in vitro (1), and impaired tumor suppressor p53 function in colon cancer cells (2). Reproductive toxicity was observed with significant decreases in sperm motility, capacitation, and fertilization rates at concentrations of 5-50 µM (3). Embryo mortality in zebrafish occurred at 7.5 µM and 12.5 µM (4). Hepatotoxicity was reported in clinical cases of severe hepatitis linked to curcumin intake (7), and animal studies showed liver toxicity at dietary levels exceeding 30% turmeric (8). General side effects included gastrointestinal disturbances at doses of 900 to 3600 mg/day (9).

Conclusion: While curcumin has beneficial anti-inflammatory and antioxidant properties, its use at higher doses poses significant risks, including DNA damage, reproductive toxicity, and hepatotoxicity. These findings underscore the necessity for cautious use of curcumin, particularly in high doses and over extended periods. Future research should focus on long-term studies to establish a comprehensive benefit-risk profile for curcumin.

Keywords: Curcumin, Turmeric, Carcinogenic Effects, Reproductive Toxicity, Hepatotoxicity, DNA Damage.

INTRODUCTION

Curcumin, derived from the root of the turmeric plant (Curcuma longa), is a bright orange-yellow compound that has been extensively used in Asian cuisine, as well as in Indian and Chinese traditional medicine. It is recognized for its therapeutic properties in various inflammatory and oxidative conditions, albeit at low doses. Despite its beneficial effects, curcumin has been shown to have limited therapeutic efficacy when ingested orally due to its poor bioavailability, leading to minimal absorption outside the alimentary tract. In high doses, curcumin has exhibited several adverse effects in both in vitro and in vivo studies, highlighting the

need for a cautious approach to its use. For instance, curcumin induces DNA alterations that may lead to carcinogenic effects, particularly through the inactivation of p53, an anti-apoptotic protein, and the activation of reactive oxygen species (ROS), which collectively contribute to cancer progression (1, 2).

Despite its long history of use, there is growing evidence that curcumin may not be entirely safe. Various studies have pointed out that while curcumin can exhibit chemopreventive properties at low doses, its high-dose administration has been linked to adverse effects such as hepatotoxicity, gastrointestinal disturbances, and alterations in reproductive functions. For example, curcumin was found to increase serum levels of alkaline phosphatase and lactate dehydrogenase, causing nausea and diarrhea in clinical trials at doses ranging from 900 to 3600 mg/day over a period of 1-4 months (3). Moreover, curcumin's low oral bioavailability necessitates its use in conjunction with black pepper to enhance absorption, which can, however, interact with various medications and further complicate its safety profile (4).

Animal studies have revealed mixed outcomes regarding curcumin's toxicity. While high doses of turmeric and curcumin have shown no adverse effects in monkeys, guinea pigs, and rats, toxicity has been observed in rats and mice when administered at doses exceeding 30% of their diet (5). Moreover, reproductive toxicity has been documented, with curcumin causing significant reductions in sperm motility, capacitation, and fertilization rates in vitro, and inducing embryo mortality in zebrafish and mouse models (6, 7). These findings underscore the potential risks associated with curcumin, particularly at higher doses.

Additionally, curcumin has been implicated in promoting lung cancer in mice and causing inflammations, ulcers, and hyperplasia in various organs when administered at high doses over prolonged periods (8, 9). It also exhibits dual roles in cancer treatment, displaying both tumor-promoting and anti-tumor properties depending on the dose and the context of its use. For instance, curcumin has been shown to activate apoptotic signals in various cancer cell lines, yet prevent apoptosis in normal cells and certain cancer cell types under specific conditions (10).

The complexity of curcumin's effects is further illustrated by its interaction with drug-metabolizing enzymes, where it inhibits cytochrome P450, glutathione-S-transferase, and UDP-glucuronosyltransferase, thereby potentially leading to drug toxicity (11). These multifaceted interactions emphasize the necessity for more comprehensive studies to delineate curcumin's safety profile, particularly concerning its long-term use and high-dose administration.

In conclusion, while curcumin has garnered significant attention for its therapeutic potential, it should be approached with caution. Its low systemic bioavailability, propensity to induce DNA alterations, oxidative stress, and suppression of p53, along with its interaction with other drugs and the induction of various pathophysiological effects at higher doses, warrant careful consideration. Future research should aim to elucidate the benefit-risk profile of curcumin, ensuring its safe application in clinical settings (12).

MATERIAL AND METHODS

The methodology for this review was designed to comprehensively assess the existing literature on the effects of curcumin, particularly focusing on its potential carcinogenic, reproductive, and hepatotoxic properties. A systematic approach was adopted to ensure the inclusion of relevant studies and accurate data extraction.

A thorough search was conducted using multiple electronic databases, including PubMed, Scopus, and Web of Science, to identify peer-reviewed articles published up to the date of the review. The search terms used included "curcumin," "turmeric," "carcinogenic," "miscarriage," "hepatotoxicity," and related keywords. Boolean operators (AND, OR) were utilized to combine search terms effectively, ensuring a comprehensive retrieval of relevant literature. Only articles published in English were considered.

The inclusion criteria for the review were as follows: studies that investigated the biological effects of curcumin in vitro, in vivo, and in clinical settings; studies that specifically addressed the carcinogenic, reproductive, and hepatotoxic effects of curcumin; and studies that provided detailed methodology and results. Exclusion criteria included articles that did not focus on the adverse effects of curcumin, review articles, and studies with insufficient methodological detail.

The initial search yielded a substantial number of articles, which were then screened based on their titles and abstracts. Full-text articles of potentially relevant studies were retrieved and further assessed for eligibility. Data were extracted independently by multiple reviewers to minimize bias and ensure accuracy. Extracted data included study design, sample size, dosage and duration of curcumin administration, observed adverse effects, and conclusions.

Quality assessment of the included studies was performed using standardized tools appropriate for different study designs. For in vitro and in vivo studies, parameters such as sample preparation, experimental controls, and outcome measures were evaluated. For clinical studies, aspects such as randomization, blinding, sample size calculation, and statistical analysis were critically appraised. The extracted data were synthesized qualitatively, and the findings were presented in a narrative format. Tables and figures were used to summarize the key characteristics and results of the included studies. The review also discussed the potential mechanisms

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underlying the adverse effects of curcumin, integrating evidence from molecular and cellular studies to provide a comprehensive understanding of its toxicological profile.

The methodology ensured a rigorous and systematic examination of the literature, providing a robust foundation for evaluating the safety and potential risks associated with curcumin consumption (1, 2, 3).

RESULTS

The review of literature on the potential adverse effects of curcumin revealed a range of findings across various in vitro, in vivo, and clinical studies. These findings were categorized into different adverse effects, including carcinogenic, reproductive, and hepatotoxic properties, as well as general side effects observed at different dosages.

Numerous studies have reported the carcinogenic potential of curcumin. It has been shown to induce DNA damage and chromosomal aberrations under specific conditions. In a study conducted by Goodpasture and Arrighi, curcumin at a dose of 10 µg/mL caused DNA strand scission in mammalian cells, suggesting a carcinogenic risk (1). Another study by Moos et al. found that curcumin impaired the tumor suppressor function of p53 in colon cancer cells, highlighting its potential to promote cancer (2).

Curcumin exhibited significant reproductive toxicity in several studies. In an in vitro study, curcumin caused a concentration-dependent decrease in sperm motility, capacitation, and fertilization rates in both human and murine sperm (3). Further, an in vivo study on zebrafish embryos demonstrated embryo mortality at concentrations of 7.5 µM and 12.5 µM (4). Curcumin was also found to induce apoptosis in mouse embryonic stem cells and blastocysts, negatively affecting oocyte maturation and fetal development (5, 6).

The hepatotoxic potential of curcumin was evident from several studies. Luber et al. reported severe hepatitis in two patients who were taking curcumin along with other medications, suggesting an interaction that led to liver damage (7). Another study by Chainani-Wu observed hepatotoxicity in mice fed with a diet containing more than 30% turmeric (8).

Various clinical studies reported general side effects of curcumin at high doses. At doses of 900 to 3600 mg/day for 1-4 months, subjects experienced increased serum levels of alkaline phosphatase and lactate dehydrogenase, along with nausea and diarrhea (9). Epidemiological data suggested a link between high dietary intake of turmeric (~150 mg/day) and the incidence of gastrointestinal cancers (10).

Table 1 Curcumin Doses in Different Studies

Study	Dosage & Duration	Subjects	Toxicity/Safety	Effects	References
Lopez-Lazaro et al. (2007)	900 to 3600 mg/day for 1-4 months	Humans	Toxicity	Increase in serum alkaline phosphatase and lactate dehydrogenase, nausea, diarrhea	(9)
Sharma et al. (2004)	~150 mg/day	Humans	Toxicity	Gastrointestinal malignancies	(10)
Mancuso & Barone (2009); Lopez-Lazaro (2008); Syng-Ai et al. (2004)	5-50 µM for a few hours	In vitro	Safety	Anticancer properties	(11)
Naz (2011)	5-15 min	Mouse germ cells	Toxicity	Ceased transcription mechanism, increased apoptosis	(3)
Shiau et al. (2011)	3 days at 7.5 µM, 2 days at 12.5 µM	Zebrafish embryos and larvae	Toxicity	Embryo mortality	(4)
Chainani-Wu (2003)	1.8 mg/kg and 0.8 mg/kg per day	Animals (monkeys, guinea pigs, rats)	Safety	No effect	(8)

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Study	Dosage & Duration	Subjects	Toxicity/Safety	Effects	References
Chainani-Wu (2003)	14 days and 90 days at 5 mg dose	Female Swiss mice and Wister rats	Toxicity	Initial toxicity in mice, later toxicity in rats	(8)
Chainani-Wu (2003)	14 days	Mice	Toxicity	Liver toxicity	(8)
Chainani-Wu (2003)	1.1-8.0 g	Humans	Safety	No toxic effects	(12)
Lao et al. (2006)	4-12 mg/day	Humans	Safety	No toxic effects	(13)
Chen & Chan (2012)	20-40 µM	Mouse reproductive cells	Toxicity	Cytotoxic to embryonic stem cells and blastocysts	(5)
Chen & Chan (2012)	24 µM for 24 hrs	Mouse embryo	Toxicity	Cytotoxic to blastocysts	(6)
Luber et al. (2014)	-	Humans	Toxicity	Severe hepatitis	(7)
Chen & Chan (2012)	12 g per day	Humans	Safety	No toxic effects	(14)
Chen & Chan (2012)	20-40 µM	Mouse oocytes	Toxicity	Reduced fertilization, decreased maturation	(5)
Chen & Chan (2012)	40 µM	Mouse fetuses	Toxicity	Lower fetal weights	(5)
Chen & Chan (2012)	30–60 µM for 24 hrs	Human melanoma	Toxicity	Apoptosis induction	(5)
Chen & Chan (2012)	10–40 µM for 16–24 hrs	Human leukemia HL 60	Toxicity	Apoptosis induction	(5)
Chen & Chan (2012)	10 µM for 18 hrs	AK-5 tumor cells	Toxicity	Apoptosis induction	(5)
Chen & Chan (2012)	25 µM for 24 hrs	MCF-7 breast cancer cells	Toxicity	Apoptosis induction	(5)
Chen & Chan (2012)	10 µM for 12 hrs	Rat thymocytes	Safety	Prevention of apoptosis induced by dexamethasone	(5)
Chen & Chan (2012)	10 µM for 12 hrs	Breast cancer cells	Safety	Prevention of apoptosis induced by chemotherapy	(5)
Chen & Chan (2012)	10 µM for 12 hrs	Mouse embryonic stem cells	Safety	Prevention of apoptosis induced by methylglyoxal	(5)
Chen & Chan (2012)	-	Human osteoblasts	Toxicity	Cytotoxic role	(5)

These findings collectively illustrate the dual nature of curcumin, demonstrating both beneficial and potentially harmful effects depending on the dosage and duration of exposure. The review emphasizes the need for further research to establish a comprehensive benefit-risk profile for curcumin, particularly at high doses and over extended periods.

DISCUSSION

The findings of this review highlighted the complex and multifaceted effects of curcumin, emphasizing its dual role as both a beneficial compound in certain contexts and a potential risk factor in others. Curcumin, a bioactive compound derived from turmeric, has been traditionally celebrated for its anti-inflammatory and antioxidant properties. However, its therapeutic efficacy is significantly limited by its poor bioavailability when ingested orally, which restricts its systemic absorption and, consequently, its effectiveness in treating various conditions (13, 14)

Previous studies have documented curcumin's chemopreventive properties at low doses, attributing its benefits to its ability to modulate multiple cellular pathways involved in inflammation and oxidative stress (15). However, at higher doses, curcumin exhibited several adverse effects, including DNA damage, reproductive toxicity, and hepatotoxicity. For instance, in vitro studies

demonstrated that curcumin could induce DNA strand breaks and chromosomal aberrations, which are precursors to carcinogenesis This carcinogenic potential was further corroborated by findings that curcumin impaired the tumor suppressor function of p53, thereby facilitating cancer progression in certain contexts (16).

Reproductive toxicity of curcumin was another critical concern identified in this review. Curcumin caused significant decreases in sperm motility, capacitation, and fertilization rates in vitro, indicating its potential to adversely affect male fertility (17). Additionally, studies on zebrafish embryos and mouse blastocysts revealed that curcumin induced embryo mortality and inhibited oocyte maturation, further underscoring its detrimental effects on reproductive health These findings suggest that curcumin, despite its traditional use in enhancing fertility, might pose significant risks to reproductive health when consumed in high doses or over extended periods.

Hepatotoxicity associated with curcumin was evident from several clinical and animal studies. Cases of severe hepatitis were reported in patients taking curcumin along with other medications, pointing to possible drug interactions that exacerbate liver injury (18). In animal models, curcumin-induced liver toxicity manifested as increased serum levels of liver enzymes and histopathological changes, indicating hepatic damage (19). These hepatotoxic effects raise significant concerns regarding the safety of curcumin, especially when used in conjunction with other drugs metabolized by the liver.

The review also highlighted the general side effects of curcumin, such as gastrointestinal disturbances, nausea, and diarrhea, particularly at higher doses (20). Epidemiological studies linking high dietary intake of turmeric to gastrointestinal malignancies further support the notion that curcumin's safety profile is dose-dependent (21). These findings align with the general understanding that while curcumin is safe at low doses, its long-term safety at high doses remains questionable.

A major strength of this review was its comprehensive approach in synthesizing data from diverse studies, providing a holistic view of curcumin's effects. However, there were notable limitations, including the variability in study designs, dosages, and durations across the included studies, which may have contributed to inconsistent findings. Furthermore, the reliance on in vitro and animal studies, which may not fully extrapolate to human scenarios, highlighted the need for more robust clinical trials to ascertain curcumin's safety and efficacy in humans.

CONCLUSION

In conclusion, while curcumin holds promise for its anti-inflammatory and antioxidant properties, its potential adverse effects at higher doses warrant cautious use. The review underscores the necessity for more rigorous long-term studies to elucidate the dose-response relationship and establish a comprehensive benefit-risk profile for curcumin. Future research should focus on addressing the limitations of current studies, exploring the molecular mechanisms underlying curcumin's adverse effects, and evaluating its safety in diverse populations. Such efforts would provide clearer guidelines for the safe and effective use of curcumin in clinical practice.

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