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Review Article

Therapeutic potential of *Euphorbia tirucalli* L. (bone-breaking tree): a comprehensive literature review

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ABSTRACT

Nasopharyngeal carcinoma (NPC) is a malignancy with high prevalence in Southeast Asia, including Indonesia, in which oxidative stress, chronic inflammation, and dysregulated cellular proliferation play important roles in carcinogenesis. Exposure to carcinogenic substances, such as formaldehyde, can induce excessive production of reactive oxygen species (ROS), resulting in cellular damage, genomic instability, and abnormal proliferation. *Euphorbia tirucalli* L. (bone-breaking tree) is a medicinal plant that has attracted considerable attention due to its diverse phytochemical composition and broad range of biological activities. Bioactive constituents, including polyphenols, flavonoids, diterpenes, triterpenes, and ellagic acid, have been reported to exhibit antioxidant, anti-inflammatory, and antiproliferative properties. Experimental studies have demonstrated that *E. tirucalli* extracts can scavenge free radicals, modulate oxidative stress pathways, suppress pro-inflammatory mediators such as NF-κB, TNF-α, and IL-6, and inhibit cancer cell proliferation through apoptosis induction. These findings suggest that *E. tirucalli* may exert chemopreventive effects through the regulation of oxidative stress, inflammation, and cellular proliferation. Nevertheless, current evidence remains largely limited to in vitro and animal studies. Further investigations focusing on molecular mechanisms, safety profiles, pharmacokinetic characteristics, and clinical efficacy are required to establish its therapeutic potential and support its future application as a chemopreventive agent, particularly in nasopharyngeal carcinogenesis.

Keywords: *Euphorbia tirucalli*, Nasopharyngeal carcinoma, Antioxidant, Chemoprevention

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a malignant epithelial neoplasm arising from the nasopharyngeal mucosa with high prevalence, particularly in Asia, including Indonesia. The carcinogenic process within the nasopharyngeal epithelium is affected by several different factors, one of which is exposure to carcinogenic substances, such as formaldehyde. Formaldehyde exposure can induce oxidative stress and chronic inflammation, resulting in excessive production of reactive oxygen species (ROS) that exceeds the capacity of the body's antioxidant defense system. Consequently, cellular damage, genomic instability, and abnormal cellular proliferation may occur, thereby promoting carcinogenesis.[1]

Several studies have demonstrated that *Euphorbia tirucalli* L. possesses antioxidant, anti-inflammatory, and anticancer activities.[2,3] Active compounds, such as ellagic acid, exhibit antiproliferative effects and have the ability to induce apoptosis in various cancer cell types, including lung, breast, prostate, liver, and colorectal cancers.[4,5] Anti-inflammatory activity has also been observed through suppression of pro-inflammatory cytokines, including TNF-α and IL-6.[5]

Based on previous findings, *Euphorbia tirucalli* L. demonstrates considerable potential as a chemopreventive agent in the carcinogenic process. Therefore, this review aims to evaluate the protective mechanisms of *E. tirucalli* branch ethanol extract against carcinogenesis in the nasopharyngeal epithelium through modulation of oxidative stress, inflammation, and cellular proliferation pathways.

MOLECULAR TARGETS IN CARCINOGENESIS: ROLE OF OXIDATIVE STRESS AND INFLAMMATION

Oxidative stress is a predominant feature in the pathophysiology of cancer. Current research increasingly recognizes ROS as a key driver of carcinogenesis and a crucial mediator in carcinogenesis.[1] The biological effects of ROS depend on the type and concentration of reactive species generated within the cellular environment.[6] ROS consist primarily of three major species: superoxide anion ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), and hydroxyl radical (•OH), the latter being the most reactive.[6]

To counteract ROS-induced damage, endogenous antioxidant enzymes, including superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx), function to neutralize these ROS species.[6] SOD serves as the first line of defense by catalyzing the conversion of superoxide anions into hydrogen peroxide, which is subsequently converted into less reactive molecules by catalase and GPx.[6,7]

In addition to regulating ROS levels, SOD also participates in several signaling pathways associated with oxidative stress reduction, including the regulation of transcription factors such as NF-κB, Nrf2, and Sp1, which play important roles in inflammation and cancer cell survival.[7] SOD can also suppress mitogen-activated protein kinase (MAPK) activation and reduce the expression of adhesion molecules involved in inflammatory responses.[7]

Furthermore, SOD contributes to Wnt signaling and cellular energy metabolism regulation, both of which are associated with tumorigenesis and therapeutic resistance.[9] That said, deficiency of SOD may lead to excessive ROS accumulation, DNA damage, and carcinogenesis.[1,6] However, cancer cells often adapt by enhancing their antioxidant capacity to support continued proliferation and survival.

EUPHORBIA TIRUCALLI L.: PHYTOCHEMICAL BASIS FOR THERAPEUTIC ACTIVITY

Euphorbia tirucalli L. is a promising plant due to its diverse phytochemical composition and broad range of biological activities. The therapeutic potential of this plant is believed to be closely associated with the presence of various bioactive compounds distributed throughout its branches, stems, and leaves.[8]

Among the phytochemical constituents identified in *E. tirucalli*, polyphenolic compounds represent an important group of bioactive substances. One of the most extensively studied compounds is ellagic acid, a naturally occurring polyphenol that has been widely associated with antioxidant, anti-inflammatory, and anticancer activities.[4] The presence of ellagic acid contributes to the growing interest in *E. tirucalli* as a potential source of natural therapeutic agents.[4,8]

Phytochemical analyses have revealed that *E. tirucalli* contains a diverse array of secondary metabolites, including flavonoids, diterpenes, steroids, alkaloids, tannins, and terpenes. In addition, several specific compounds have been identified, such as α-euphorbol, euphol, tirucallol, taraxasterol, n-hexacosanol, and cycloeuphornol.[8] The diversity of these phytochemical constituents suggests that *E. tirucalli* possesses a complex chemical profile that may contribute to its pharmacological properties.[8]

Furthermore, methanolic and aqueous extracts derived from the leaves and stems of *E. tirucalli* have been reported to contain high concentrations of phenolic compounds and flavonoids.[3] The abundance of these phytochemicals has attracted considerable research interest and provides an important foundation for understanding the biological activities and therapeutic potential of this plant.

ANTIOXIDANT MECHANISMS OF *EUPHORBIA TIRUCALLI*

E. tirucalli extracts, particularly methanolic and aqueous extracts obtained from leaves and stems, have consistently demonstrated strong antioxidant activity through various assays, including DPPH radical scavenging, superoxide scavenging, and hydroxyl radical scavenging assays.[3,9,10] These antioxidant effects are largely attributed to the high concentrations of phenolic compounds and flavonoids present in the plant extracts.[3]

Physiologically, antioxidant defense mechanisms involve enzymes, such as SOD, GPx, and catalase, which maintain oxidant-antioxidant homeostasis within cells.[6] However, under pathological conditions, ROS production may exceed endogenous antioxidant defenses, resulting in cellular dysfunction.[1]

An in vivo study by Jyothi et al. showed that *E. tirucalli* ethanol extract has a protective mechanism through oxidative stress level regulation, anti-inflammation, and cellular apoptosis in Wistar rats. The study also reported that oral administration of *E. tirucalli* ethanol extract at doses of 125–250 mg/kg/day produced significant antioxidant effects.[9]

In this context, exogenous antioxidants derived from medicinal plants such as *E. tirucalli* may contribute to

neutralizing free radicals, restoring oxidative balance, and protecting tissues from oxidative injury.[1,6,9]

ANTI-INFLAMMATORY AND ANTIPROLIFERATIVE EFFECTS

Formaldehyde exposure induces inflammatory responses through activation of multiple signaling pathways, including NF-κB-mediated TNF-α production. Persistent NF-κB activation induces chronic inflammation and mucosal damage, which subsequently facilitates cancer cell proliferation, inhibits apoptosis, increases drug resistance, stimulates angiogenesis, and enhances tumor metastasis.[11]

In addition to inflammatory mediators, markers of cellular proliferation also play an important role in the process of carcinogenesis. Under conditions of cellular stress caused by DNA damage, Ki-67 expression is associated with cellular proliferation status and may reflect the balance between DNA repair and apoptotic pathways. If DNA damage cannot be adequately repaired, apoptotic mechanisms are activated to prevent propagation of genetically unstable cells.[12]

Studies involving ethanol extracts of *E. tirucalli* branches have revealed cytotoxic effects against T47D breast cancer cells and significant inhibition of cancer cell proliferation *in vitro*.[13] Additionally, anti-inflammatory activity has been observed through suppression of nitric oxide production and pro-inflammatory mediators such as NF-κB, TNF-α, and IL-6 in lipopolysaccharide-induced macrophages in several cancer cell models.[5] Ellagic acid has likewise demonstrated antiproliferative effects and apoptosis induction across several cancer cell lines, including lung, breast, prostate, liver, and colorectal cancers.[4]

THERAPEUTIC POTENTIAL AND LIMITATIONS

Euphorbia tirucalli L. is a natural product with considerable potential for development as a therapeutic agent due to its high flavonoid content, widespread availability, affordability, and extensive investigation in previous studies. Various studies have demonstrated that ethanol extracts of *Euphorbia tirucalli* branches possess antioxidant, anti-inflammatory, and anticancer activities.

In addition, preclinical studies have demonstrated biological activity following administration of *E. tirucalli* extracts at doses ranging from 125–250 mg/kg/day, supporting its potential therapeutic application.[9] These findings suggest the potential application of *Euphorbia tirucalli* L. as a chemopreventive agent through mechanisms involving oxidative stress modulation, inflammation suppression, and regulation of cellular proliferation.

Nevertheless, the use of *Euphorbia tirucalli* L. also has certain limitations. Several studies have reported potential toxic and harmful effects associated with specific parts of the plant. Therefore, its utilization as a therapeutic agent should be approached with careful consideration of safety aspects and appropriate dosage regimens.[9]

RESEARCH GAP AND FUTURE PERSPECTIVE

Research on the role of antioxidants in the carcinogenic process of the nasopharyngeal mucosal epithelium has been widely conducted; however, studies simultaneously investigating the relationship among oxidative stress, inflammation, and cellular proliferation remain limited. Furthermore, studies evaluating TNF-α and Ki-67 levels in relation to carcinogenesis of the nasopharyngeal mucosal epithelium following antioxidant administration are still scarce.[1,11,14]

Though several previous studies have demonstrated the antioxidant, anti-inflammatory, and antiproliferative activities of *Euphorbia tirucalli* L. extracts, studies evaluating these mechanisms in a model of formaldehyde-induced nasopharyngeal carcinogenesis remain limited.[3,8,9]

Further studies focusing on the pathomechanisms underlying dysplasia of the nasopharyngeal mucosal epithelium induced by formaldehyde exposure, as well as the protective mechanisms of *Euphorbia tirucalli* L. branch ethanol extract through biomolecular pathways involving oxidative stress (assessed by SOD levels), inflammation (assessed by TNF-α expression), and cellular proliferation (assessed by Ki-67 expression), are needed.[11,14]

Such studies are essential to strengthen the scientific evidence regarding the effectiveness and safety of *Euphorbia tirucalli* L. as a chemopreventive agent, particularly in the prevention of carcinogenesis in the nasopharyngeal mucosal epithelium.

CONCLUSION

Euphorbia tirucalli L. (bone-breaking tree) has potential as a chemopreventive agent in the carcinogenic process, particularly in the nasopharyngeal mucosal epithelium following formaldehyde exposure. Bioactive compounds such as flavonoids, polyphenols, and ellagic acid contribute to its antioxidant, anti-inflammatory, and antiproliferative activities by reducing oxidative stress, suppressing inflammatory mediators, and inhibiting abnormal cellular proliferation.

Various in vitro and in vivo studies have demonstrated promising findings regarding the therapeutic potential of *Euphorbia tirucalli* L. However, scientific evidence regarding its efficacy, safety, and toxicity remains limited. Therefore, further studies are required to establish its effectiveness and safety before it can be developed as a therapeutic or chemopreventive agent for nasopharyngeal carcinogenesis.

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