World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(REVIEW ARTICLE)

Check for updates

Targeting the hallmarks of cancer: A literature review on the multi-modal anticancer properties of xanthorrhizol

Neha Ninad Shinde [1,*], Aisya Azzahra Sudarmanto [1], Danial Habri Arsyi [1] and Annette d'Arqom [1,2]

[1] *Faculty of Medicine, Universitas Airlangga, Jl. Prof. Mayjen Dr. Moestopo, 47, Surabaya East Java, 60131, Indonesia.*
[2] *Department of Pharmacology, Faculty of Medicine, Universitas Airlangga, Jl. Prof. Mayjen Dr. Moestopo, 47, Surabaya East Java, 60131, Indonesia.*

World Journal of Advanced Research and Reviews, 2025, 26(03), 742-750

Publication history: Received on 27 April 2025; revised on 04 June 2025; accepted on 06 June 2025

Article DOI: https://doi.org/10.30574/wjarr.2025.26.3.2262

Abstract

Cancer continues to be a major global health burden, necessitating the development of effective and targeted therapies. The conceptual framework of the ten hallmarks of cancer has advanced our understanding of tumor biology and guided the discovery of novel therapeutic strategies. Natural products, particularly phytochemicals, have emerged as a valuable source of anticancer agents due to their biological activity. One such compound is xanthorrhizol, a bioactive sesquiterpenoid extracted from Curcuma xanthorrhiza. This literature review explores the anticancer mechanisms of xanthorrhizol through the lens of the hallmarks of cancer, providing a structured overview of current experimental findings and identifying gaps for future investigation. Xanthorrhizol exerts broad anticancer effects through its influence on multiple cancer hallmarks, namely proliferation, apoptosis, angiogenesis, inflammation, and metastasis. While promising, more mechanistic and clinical studies are needed to validate its use as an anticancer therapy.

Keywords: Xanthorrhizol; Cancer; Cancer Hallmark; Proliferation; Malignancy; Apoptosis

1. Introduction

Cancer is a complex and life-threatening disease characterized by the uncontrolled growth and division of abnormal cells in the body. It encompasses over 200 distinct disease types, each with its own molecular profile, clinical behavior, and response to treatment [1-2]. Despite decades of intensive research and the development of therapies, cancer remains a leading cause of morbidity and mortality worldwide. In 2022 alone, 20 million new cancer cases and 9.7 million cancer-related deaths occurred worldwide [3].

The progression and persistence of cancer are driven by a set of biological traits, referred to as the hallmarks of cancer, initially proposed by Hanahan and Weinberg in 2000 and later expanded in 2011 [4,5]. These hallmarks include sustained proliferative signaling, evasion of growth suppressors, resistance to cell death, replicative immortality, induction of angiogenesis, and activation of invasion and metastasis. In addition to these original six hallmarks, four emerging hallmarks have been identified to further define the malignant phenotype: deregulating cellular energetics, avoiding immune destruction, genome instability and mutation, and tumor-promoting inflammation [5]. Together, these hallmarks provide a comprehensive framework for understanding tumor biology and serve as a foundation for the development of targeted cancer therapies.

Standard treatment modalities for cancer include surgery, chemotherapy, radiotherapy, and hormonal or targeted therapies. While these approaches have significantly improved survival outcomes, several critical limitations persist. Cancer cells are highly adaptive, often developing resistance to chemotherapeutic agents through genetic and epigenetic

* Corresponding author: Neha Ninad Shinde.

modifications. Additionally, conventional treatments are frequently associated with significant toxicity, leading to a compromised quality of life and poor treatment adherence. In low- and middle-income countries, these challenges are compounded by socioeconomic disparities and restricted access to specialized oncologic care, which collectively hinder treatment continuity and patient adherence. The financial burden of long-term therapy further exacerbates inequities in care delivery. Consequently, there is a growing interest in exploring more accessible, safer, and cost-effective alternatives, including bioactive compounds derived from traditional medicinal plants that are culturally integrated and widely available. These challenges underscore the urgent need for alternative or adjunctive therapies that are effective, less toxic, and more accessible [6].

One such compound is xanthorrhizol, a bisabolane-type sesquiterpenoid isolated from Curcuma xanthorrhiza, which is traditionally used in Southeast Asian medicine to treat various ailments such as digestive disorders, bacterial infections, fever, and arthritis [7]. Xanthorrhizol has demonstrated a wide range of biological activities, including anti-inflammatory, antimicrobial, antioxidant, and notably, anticancer effects [8]. Given its abundance and potential for large-scale extraction, xanthorrhizol represents a cost-effective and accessible alternative or adjunctive therapy for cancer. Therefore, in this review, we explore the potential of xanthorrhizol as a multi-targeted anticancer agent through the lens of the hallmarks of cancer. By organizing current literature findings around each hallmark, we aim to highlight the mechanistic basis of xanthorrhizol's activity, identify therapeutic implications, and underscore its promise as a candidate for integrated cancer treatment strategies.

2. Methods

This review employed a narrative literature review approach to synthesize current evidence on the anticancer effects of xanthorrhizol, particularly in relation to the hallmarks of cancer. A comprehensive search was conducted using scientific databases including PubMed, Google Scholar, and ScienceDirect. Search terms included combinations of keywords such as "xanthorrhizol," "Curcuma xanthorrhiza," "cancer," "anticancer," "hallmarks of cancer," "cell cycle," "apoptosis," "angiogenesis," and "metastasis." Only articles published in English and Indonesian were included. Eligible studies were selected based on their investigation of the pharmacological properties of xanthorrhizol, including in vitro, in vivo, and selected clinical studies.

The findings were synthesized thematically according to the ten biological hallmarks of cancer described by Hanahan and Weinberg [5]. This framework guided the structured discussion of the molecular mechanisms and therapeutic potential of xanthorrhizol across multiple cancer-related processes.

3. Results and Discussion

3.1. Cancer pathogenesis

Cancer arises from a series of molecular and cellular alterations that disrupt the tightly regulated mechanisms controlling cell growth, differentiation, and death. These changes are often driven by the accumulation of somatic mutations, which are acquired and occur over a person's lifetime, and, in some cases, germline mutations, which are inherited and may predispose individuals to specific cancer types [9]. For instance, germline mutations in the BRCA1 and BRCA2 genes significantly increase the risk of developing hereditary breast and ovarian cancers, with lifetime risks as high as 72% and 69%, respectively [9–10]. Inherited mutations in genes such as TP53, APC, MLH1, and RET have also been implicated in a range of other cancers including colorectal, endocrine, and soft tissue tumors [11]

Beyond inherited susceptibility, the vast majority of cancers are sporadic and arise due to environmental exposures (e.g., carcinogens, radiation, infections), lifestyle factors (e.g., smoking, diet, obesity), and errors in DNA replication. These mutational events can activate oncogenes, inactivate tumor suppressor genes, and interfere with DNA repair mechanisms, ultimately leading to the breakdown of cellular homeostasis [12]. As a result, cells begin to acquire features that confer survival advantages in the hostile tumor microenvironment.

Hanahan and Weinberg's framework of the hallmarks of cancer distills the complex processes of carcinogenesis into ten defining traits, with each of them reflecting a specific functional capability that cancer cells acquire to sustain growth, resist elimination, and invade surrounding tissues [5].

3.2. Current management of cancer

Cancer management has significantly advanced over the past few decades through the adoption of multidisciplinary treatment strategies tailored to tumor type, stage, molecular profile, and patient-specific factors. Standard therapeutic

modalities include surgery, chemotherapy, radiotherapy, immunotherapy, hormonal therapy, and molecularly targeted agents. Treatment selection is generally guided by parameters such as tumor size, histological grade, metastatic spread, and the presence of actionable molecular or receptor-based biomarkers (e.g., hormone receptors, epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), PD-L1, and others) [13-14].

Surgical resection remains a cornerstone of curative therapy for many solid tumors, including breast, colorectal, lung, and head and neck cancers [15]. Depending on tumor location and extent, procedures may range from organ-sparing surgeries to radical resections. While surgery often offers the best chance for long-term survival in localized cancers, it is not without complications. Patients may face risks such as postoperative infection, bleeding, seroma formation, or organ dysfunction [16]. Moreover, long-term physical and psychosocial effects, such as altered body image, chronic pain, or reduced mobility, can significantly impact quality of life. For example, in breast and head and neck cancers, postoperative appearance changes have been associated with higher rates of anxiety, depression, and social withdrawal. Surgical procedures also carry risks of skin necrosis [17-20].

Chemotherapy plays a central role in both curative and palliative settings. It is commonly used as neoadjuvant therapy to reduce tumor burden before surgery or as adjuvant therapy to eliminate micrometastatic disease and prevent recurrence. Standard regimens often include agents such as platinum compounds, anthracyclines, and taxanes. However, chemotherapy is associated with systemic toxicity, including myelosuppression, nausea, fatigue, alopecia, mucositis, and neuropathy, all of which can hinder adherence and quality of life. Long-term cardiac dysfunction is a notable concern with anthracycline-based therapies, with studies reporting subclinical cardiac abnormalities and increased risk of heart failure years after treatment [21-22].

Hormonal therapy is employed in cancers driven by hormone signaling, such as breast, prostate, and endometrial cancers [23]. Agents like tamoxifen, aromatase inhibitors, or androgen deprivation therapy are effective in reducing recurrence and progression. However, their long-term use is often accompanied by adverse effects such as menopausal symptoms, decreased libido, hot flashes, thromboembolic events, and bone demineralization, which may impair treatment adherence [24-25].

Emerging treatment strategies such as immune checkpoint inhibitors, CAR-T cell therapy, and targeted therapies (e.g., tyrosine kinase inhibitors, monoclonal antibodies) have transformed the landscape of oncology, particularly in malignancies such as melanoma, non-small cell lung cancer, and hematologic cancers. Nevertheless, these treatments also carry risks of immune-related adverse events, resistance mechanisms, and high financial burden, all of which require careful consideration in clinical decision-making [26-27].

3.3. Traditional management of cancer

Table 1 Hallmark-Specific Antitumor Actions of Xanthorrhizol

Hallmark of Cancer	**Molecular Targets & Mechanisms**	**Model Evidence**	**References**
Resisting cell death	Activation of caspase-3, -8, -9; increased Bax/Bcl-2 ratio; upregulation of tumor suppressor p53	MDA-MB-231 and MCF-7 breast cancer cells, HeLa cervical cancer cells, HepG2 liver cancer cells	29, 30, 31, 32, 33
Sustaining proliferative signaling	Downregulation of cyclin D1, CDK4/6; suppression of EGFR expression	HCT116 colon cancer cells, MDA-MB-231 breast cancer cells, murine B16 melanoma cells, human DU145 prostate carcinoma cells	34, 35, 36
Evading growth suppressors	No reported activity	-	-
Enabling replicative immortality	No reported activity	-	-
Inducing angiogenesis	Downregulation of VEGF and HIF-1α; reduced microvessel density	Mouse xenograft models with MDA-MB-231, HUVECs	37

Activating invasion and metastasis	Inhibition of MMP-2, MMP-9 expression; decreased E-cadherin suppression; reduction in motility and invasiveness	Murine CT26 lung cancer cells, MDA-MB-231 breast cancer cells	34, 38
Deregulating cellular energetics	Increased ROS	SCC-15 oral squamous cell carcinoma	39
Avoiding immune destruction	No reported activity	-	-
Genome instability and mutation	No reported activity	-	-
Tumor-promoting inflammation	Inhibition of NF-κB, COX-2 and iNOS expression	LPS-induced RAW264.7 macrophages	40

CDK = cyclin-dependent kinases; EGFR = epidermal growth factor receptor; VEGF = vascular endothelial growth factor; HIF-1α = Hypoxia-Inducible Factor-1 alpha; HUVEC = human umbilical vein endothelial cells; MMP = matrix metalloproteinases; ROS = reactive oxygen species; NF-κB = nuclear factor kappa B; COX-2 = cyclooxygenase-2; iNOS = inducible nitric oxide synthase; LPS = lipopolysaccharide

Natural plant products, such as ginseng, turmeric, flaxseed, xanthorrhizol, and garlic, have been used for centuries in the treatment of various ailments [28]. In cancer management, while surgery, chemotherapy, radiotherapy, and hormonal therapies remain the mainstays, increasing attention has been given to plant-derived compounds for their potential to complement conventional treatments. Among these, xanthorrhizol has attracted significant scientific interest due to its multi-targeted anticancer effects. Several studies have investigated its role in modulating key biological processes involved in cancer progression, making it a promising candidate for further research and potential therapeutic use [29-40]. Evidence presented in these studies suggests that xanthorrhizol interferes with several core mechanisms that underlie cancer development and progression, including unchecked cell proliferation, evasion of growth suppression, resistance to apoptosis, and other defining traits of malignancy. Mapping xanthorrhizol's activity onto these processes can offer insight into how it exerts therapeutic effects across multiple cellular pathways.

Xanthorrhizol has demonstrated promising anticancer properties through its effects on key hallmarks of cancer. Based on available evidence, xanthorrhizol primarily targets several well-characterized hallmarks, including resisting cell death, sustaining proliferative signaling, inducing angiogenesis, activating metastasis, deregulating cellular energetics, and promoting inflammation.

3.4. Resisting cell death

Under normal physiological conditions, cells undergo programmed cell death to eliminate damaged, dysfunctional, or potentially dangerous cells. This mechanism is crucial for maintaining tissue homeostasis and preventing malignant transformation. Apoptosis occurs via two main pathways: the intrinsic (mitochondrial) and extrinsic (death receptor-mediated) pathways. These are tightly regulated by a balance between pro-apoptotic proteins (e.g. Bax) and anti-apoptotic proteins (e.g. Bcl-2), along with a cascade of caspases. Cancer cells evade apoptosis by tipping this balance toward survival, often through overexpression of anti-apoptotic proteins or suppression of death-inducing signals. This resistance to cell death allows tumor cells to survive despite genetic damage or external therapies that would normally trigger apoptosis [41].

Xanthorrhizol has been shown to restore apoptotic sensitivity by modulating key regulatory proteins such as p53, Bax, and Bcl-2. The upregulation of pro-apoptotic factors and downregulation of anti-apoptotic proteins result in mitochondrial membrane depolarization, cytochrome c release, and subsequent caspase activation. This leads to the activation of caspase-9, followed by caspase-3. In addition, xanthorrhizol activates caspase-8, suggesting engagement of the extrinsic apoptotic pathway as well. These dual actions trigger cell death in cancer cells while sparing normal cells [29-33].

3.5. Sustaining proliferative signaling

Uncontrolled cell proliferation is a fundamental hallmark of cancer, driven by the persistent activation of growth-promoting signaling pathways. Normally, cellular proliferation is tightly regulated by extracellular signals such as

growth factors, which bind to receptors like EGFR and HER2 on the cell surface. Through activation of intracellular cascades, primarily the PI3K/Akt and MAPK/ERK pathways, cell survival, metabolism, and division are promoted [42].

Progression through the cell cycle is further regulated by proteins called cyclins and their partners, the cyclin-dependent kinases (CDKs). In particular, cyclin D1 and CDK4/6 drive the transition from the G1 phase to the S phase, committing cells to DNA replication [43]. In many cancers, these signaling and regulatory proteins are overexpressed or constitutively active, resulting in sustained, unregulated cell proliferation [44].

Xanthorrhizol demonstrates potent antiproliferative activity against cancer cells by targeting multiple nodes within the proliferative network. It induces cell cycle arrest at both G0/G1 and G2/M phases by downregulating cyclins A, B1, and D1, and their associated kinases CDK1, CDK2, and CDK4. This results in the inhibition of retinoblastoma protein (pRb) phosphorylation, preventing the release of E2F transcription factors required for S phase entry. Additionally, upregulation of CDK inhibitors such as p21 and p27 by xanthorrhizol further suppresses CDK activity, reinforcing cell cycle blockade and preventing DNA replication and mitosis [34-36].

3.6. Inhibiting angiogenesis

Angiogenesis, the formation of new blood vessels from pre-existing vasculature, is a critical process that allows tumors to secure an adequate supply of oxygen and nutrients, enabling their growth and metastatic spread. Vascular endothelial growth factor (VEGF), as a key driver in angiogenesis, stimulates the growth of blood vessels and is typically upregulated in tumors, particularly under hypoxic conditions. In response to hypoxia, cells increase the expression of hypoxia-inducible factor-1α (HIF-1α), a transcription factor that activates genes responsible for angiogenesis, including VEGF [45]. Xanthorrhizol has been shown to inhibit angiogenesis by downregulating VEGF expression and suppressing HIF-1α. It also impairs endothelial cell proliferation, migration, and tube formation, all of which are processes essential for the development of new vasculature [37].

3.7. Activating invasion and metastasis

Metastasis is a defining feature of malignant tumors and a leading cause of cancer-related mortality. This complex, multistep process involves detachment from the primary tumor mass, degradation of the extracellular matrix (ECM), intravasation into the bloodstream or lymphatics, survival in circulation, extravasation into secondary tissues, and colonization. At the molecular level, cancer cells acquire motility and invasive capabilities through epithelial-to-mesenchymal transition (EMT), which is orchestrated by transcription factors such as Snail, Slug, Twist, and ZEB1 [46-47]. This transition reduces epithelial markers (e.g., E-cadherin) and enhances mesenchymal markers (e.g., N-cadherin, vimentin), facilitating tissue invasion and dissemination [48].

Xanthorrhizol has shown efficacy in reducing metastasis-associated behaviors in breast cancer cells through the suppression of EMT via restoration of E-cadherin expression. Furthermore, xanthorrhizol inhibits the activity of matrix metalloproteinases (MMP-2 and MMP-9), which are critical for ECM degradation and metastasis. These effects are particularly relevant in aggressive tumor types, such as triple-negative breast cancer, but may extend to other cancers where nuclear factor-kappa B (NF-κB) and MMPs play a central role in metastatic spread [34, 38].

3.8. Deregulating cellular energetics

Unlike normal cells, which primarily rely on mitochondrial oxidative phosphorylation, cancer cells preferentially utilize aerobic glycolysis, a phenomenon known as the Warburg effect. This metabolic shift supports the increased biosynthetic and energetic demands of proliferating tumor cells and is regulated by factors such as HIF-1α, which promotes the expression of glycolytic genes including GLUT1, hexokinase 2, and lactate dehydrogenase A. However, this altered metabolism comes at a cost: it produces elevated levels of reactive oxygen species (ROS) as metabolic by-products. While moderate ROS levels can promote cancer cell survival by activating pro-survival pathways such as HIF-1α and GLUT1, excessive ROS leads to metabolic stress, protein damage, and cell death [49]. To counteract this, cancer cells enhance their antioxidant defense mechanisms, notably through the glutathione and thioredoxin systems, to maintain redox balance and avoid cytotoxicity. Xanthorrhizol exploits this metabolic vulnerability by further increasing ROS levels in cancer cells, tipping the redox balance toward oxidative stress-induced death [39].

3.9. Tumor-promoting inflammation

Chronic inflammation creates a tumor-permissive microenvironment by promoting cellular proliferation, inhibiting apoptosis, facilitating angiogenesis, and enabling metastatic dissemination. One of the central molecular drivers of this inflammatory state is the transcription factor NF-κB, which regulates the expression of numerous pro-inflammatory cytokines and enzymes, including cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) [50-51]. While

NF-κB plays a vital role in immune defense, its sustained activation in tumors can lead to persistent inflammation that fuels cancer cell survival and resistance to therapies [52].

Xanthorrhizol disrupts this inflammation-driven oncogenic signaling by inhibiting key pro-inflammatory mediators. Specifically, it potently suppresses the expression and activity of COX-2 and iNOS, enzymes responsible for the production of prostaglandin E2 (PGE2) and nitric oxide (NO), respectively. These inflammatory molecules contribute to DNA damage, immune evasion, and tumor-promoting angiogenesis. The inhibitory effect of xanthorrhizol on COX-2 correlates with a marked reduction in COX-2 protein expression in activated macrophages, suggesting that its anti-inflammatory action occurs at the transcriptional or translational level [40].

3.10. Future research prospects

While these findings suggest a multi-targeted mechanism, current data is insufficient to support the claim that xanthorrhizol interferes with all ten hallmarks of cancer. In contrast to more extensively studied phytochemicals such as curcumin or thymoquinone, xanthorrhizol's functional reach appears more restricted, with limited or inconclusive evidence regarding its role in particular hallmarks, including avoiding immune destruction, evading growth suppressors, enabling replicative immortality, and genome instability and mutation [53].

In line with Hanahan and Weinberg's updated hallmark framework, rational anticancer therapy may benefit from agents like xanthorrhizol that selectively target multiple cancer-enabling processes [5]. While xanthorrhizol may not serve as a broad-spectrum anticancer agent on its own, its well-documented effects on proliferation, apoptosis, and angiogenesis make it a strong candidate for inclusion in co-chemotherapy regimens [29-40]. Future studies should focus on identifying synergistic combinations of xanthorrhizol with other phytochemicals or chemotherapeutic agents and evaluating these in integrative cancer models that better reflect the complexity of tumor biology.

3.11. Safety profile

Current evidence suggests that xanthorrhizol and its source plant Curcuma xanthorrhiza exhibit a favorable safety profile in preclinical models. In acute toxicity studies, mice tolerated oral doses of xanthorrhizol up to 500 mg/kg without experiencing lethality or noticeable changes in behavior [54]. In longer-term exposure studies, daily administration of 150 mg/kg of C. xanthorrhiza extract over a 90-day period did not result in mortality or abnormalities in behavior, external morphology, hematological parameters, or spermatogenesis [56]. Taken together, these findings support the non-toxic nature of xanthorrhizol in both acute and sub-chronic settings.

Nonetheless, while these data indicate a high threshold for toxicity in animal models, critical gaps remain. The genotoxic and reproductive safety profiles of xanthorrhizol have not been thoroughly investigated. Additionally, the therapeutic window and optimal dosing in disease-specific contexts remain to be defined. More comprehensive toxicological evaluations, particularly in human-relevant systems, are necessary before clinical application can be considered.

4. Conclusion

Xanthorrhizol demonstrates considerable therapeutic potential in the treatment of cancer through its ability to target apoptosis resistance, proliferation, angiogenesis, metastasis, inflammation, and cellular energetics deregulation. Preclinical studies indicate a favorable safety profile, but comprehensive toxicological evaluations and clinical investigations are needed to fully establish its therapeutic potential. Future research should prioritize exploring synergistic combinations of xanthorrhizol with existing chemotherapeutics and natural compounds, aiming to enhance efficacy and overcome cancer complexity through integrative treatment strategies.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no conflicts of interest, financial or otherwise, that could have influenced the conduct, analysis, or interpretation of this review.

References

[1] National Health Service. Cancer [Internet]. United Kingdom: NHS; 2025 May 27 [cited 2025 June 1]. Available from: https://www.nhs.uk/conditions/cancer/

[2] Cooper GM, Adams K. The cell: a molecular approach. 9th ed. Oxford University Press; 2022.

[3] Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2024;74(3):229-63.

[4] Hanahan D, Weinberg RA. The hallmarks of cancer. Cell. 2000;100(1):57-70.

[5] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646-74.

[6] Satria D. Complementary and alternative medicine (cam): Fakta atau janji. Idea Nursing Journal. 2013;4(3).

[7] Hwang JK, Shim JS, Pyun YR. Antibacterial activity of xanthorrhizol from Curcuma xanthorrhiza against oral pathogens. 2000;71(3):321-323.

[8] Oon SF, Nallappan M, Tee TT, Shohaimi S, Kassim NK, Sa'ariwijaya MS, Cheah YH. Xanthorrhizol: a review of its pharmacological activities and anticancer properties. Cancer cell international. 2015;15:1-5.

[9] Stratton MR, Campbell PJ, Futreal PA. The cancer genome. Nature. 2009;458(7239):719-24.

[10] Kuchenbaecker KB, Hopper JL, Barnes DR, Phillips KA, Mooij TM, Roos-Blom MJ, Jervis S, Van Leeuwen FE, Milne RL, Andrieu N, Goldgar DE. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. Jama. 2017;317(23):2402-16.

[11] Futreal PA, Coin L, Marshall M, Down T, Hubbard T, Wooster R, Rahman N, Stratton MR. A census of human cancer genes. Nature reviews cancer. 2004;4(3):177-83.

[12] Golemis EA, Scheet P, Beck TN, Scolnick EM, Hunter DJ, Hawk E, Hopkins N. Molecular mechanisms of the preventable causes of cancer in the United States. Genes & development. 2018;32(13-14):868-902.

[13] Debela DT, Muzazu SG, Heraro KD, Ndalama MT, Mesele BW, Haile DC, Kitui SK, Manyazewal T. New approaches and procedures for cancer treatment: Current perspectives. SAGE open medicine. 2021;9:20503121211034366.

[14] Cufer T, Kosty MP, Curriculum Development Subgroup—ESMO/ASCO Global Curriculum Working Group. ESMO/ASCO recommendations for a global curriculum in medical oncology edition 2023. JCO Global Oncology. 2023 Oct;9:e2300277.

[15] Debela DT, Muzazu SG, Heraro KD, Ndalama MT, Mesele BW, Haile DC, Kitui SK, Manyazewal T. New approaches and procedures for cancer treatment: Current perspectives. SAGE Open Med. 2021;9:20503121211034366.

[16] Rosa F, Schena CA, Laterza V, Quero G, Fiorillo C, Strippoli A, Pozzo C, Papa V, Alfieri S. The Role of Surgery in the Management of Gastric Cancer: State of the Art. Cancers (Basel). 2022;14(22):5542.

[17] Chow R, Pulenzas N, Zhang L, Ecclestone C, Leahey A, Hamer J, DeAngelis C, Bedard G, McDonald R, Bhatia A, Ellis J. Quality of life and symptom burden in patients with breast cancer treated with mastectomy and lumpectomy. Supportive Care in Cancer. 2016;24:2191-9.

[18] Lasry JC, Margolese RG, Poisson R, Shibata H, Fleischer D, Lafleur D, Legault S, Taillefer S. Depression and body image following mastectomy and lumpectomy. Journal of chronic diseases. 1987;40(6):529-34.

[19] Wellisch DK, DiMatteo R, Silverstein M, Landsverk J, Hoffman R, Waisman J, Handel N, Waisman-Smith E, Schain W. Psychosocial outcomes of breast cancer therapies: lumpectomy versus mastectomy. Psychosomatics. 1989;30(4):365-73.

[20] Aitken DR, Minton JP. Complications associated with mastectomy. Surgical Clinics of North America. 1983;63(6):1331-52.

[21] Altun I, Sonkaya A. The most common side effects experienced by patients were receiving first cycle of chemotherapy. Iranian journal of public health. 2018;47(8):1218.

[22] Steinherz LJ, Steinherz PG, Tan CT, Heller G, Murphy ML. Cardiac toxicity 4 to 20 years after completing anthracycline therapy. Jama. 1991;266(12):1672-7.

[23] Puhalla S, Bhattacharya S, Davidson NE. Hormonal therapy in breast cancer: a model disease for the personalization of cancer care. Mol Oncol. 2012;6(2):222-36.

[24] Franzoi MA, Agostinetto E, Perachino M, Del Mastro L, de Azambuja E, Vaz-Luis I, Partridge AH, Lambertini M. Evidence-based approaches for the management of side-effects of adjuvant endocrine therapy in patients with breast cancer. The Lancet Oncology. 2021;22(7):e303-13.

[25] Desai K, McManus JM, Sharifi N. Hormonal therapy for prostate cancer. Endocrine reviews. 2021;42(3):354-73.

[26] Akunne OZ, Anulugwo OE, Azu MG. Emerging strategies in cancer immunotherapy: Expanding horizons and future perspectives. International Journal of Molecular and Immuno Oncology. 2024;9(3):77-99.

[27] Garg P, Pareek S, Kulkarni P, Horne D, Salgia R, Singhal SS. Next-Generation Immunotherapy: Advancing Clinical Applications in Cancer Treatment. J Clin Med. 2024;13(21):6537.

[28] McGrowder DA, Miller FG, Nwokocha CR, Anderson MS, Wilson-Clarke C, Vaz K, Anderson-Jackson L, Brown J. Medicinal Herbs Used in Traditional Management of Breast Cancer: Mechanisms of Action. Medicines (Basel). 2020;7(8):47.

[29] Cheah YH, Nordin FJ, Tee TT, Azimahtol HL, Abdullah NR, Ismail Z. Antiproliferative property and apoptotic effect of xanthorrhizol on MDA-MB-231 breast cancer cells. Anticancer Research. 2008;28(6A):3677-89.

[30] Cheah YH, Azimahtol HL, Abdullah NR. Xanthorrhizol exhibits antiproliferative activity on MCF-7 breast cancer cells via apoptosis induction. Anticancer research. 2006;26(6B):4527-34.

[31] Ismail N, Pihie AH, Nallapan M. Xanthorrhizol induces apoptosis via the up-regulation of bax and p53 in HeLa cells. Anticancer Res. 2005;25(3B):2221-7.

[32] Cheah YH, Nordin FJ, Sarip R, Tee TT, Azimahtol HL, Sirat HM, Rashid BA, Abdullah NR, Ismail Z. Combined xanthorrhizol-curcumin exhibits synergistic growth inhibitory activity via apoptosis induction in human breast cancer cells MDA-MB-231. Cancer Cell International. 2009;9:1-2.

[33] Kim Y, Na HJ, Kim MJ. Anti-proliferative Efficacy of Xanthorrhizol on Cancer Cells via Activation of hTAS2R38 among 25 Human Bitter Taste Receptors. Journal of the Korean Society of Food Culture. 2024;39(3):166-72.

[34] Choi MA, Kim SH, Chung WY, Hwang JK, Park KK. Xanthorrhizol, a natural sesquiterpenoid from Curcuma xanthorrhiza, has an anti-metastatic potential in experimental mouse lung metastasis model. Biochem Biophys Res Commun. 2005;326(1):210–7.

[35] Chan D, Meister ML, Madhani CR, Elfakhani M, Yount ST, Ji X, Feresin RG, Wanders D, Mo H. Synergistic Impact of Xanthorrhizol and d-δ-Tocotrienol on the Proliferation of Murine B16 Melanoma Cells and Human DU145 Prostate Carcinoma Cells. Nutr Cancer. 2021;73(9):1746-1757.

[36] Kang YJ, Park KK, Chung WY, Hwang JK, Lee SK. Xanthorrhizol, a natural sesquiterpenoid, induces apoptosis and growth arrest in HCT116 human colon cancer cells. J Pharmacol Sci. 2009;111(3):276-84.

[37] Lee SK, Kim MJ, Son SH, Kim KR, Park KK, Chung WY. Xanthorrhizol Suppresses Vascular Endothelial Growth Factor-Induced Angiogenesis by Modulating Akt/eNOS Signaling and the NF-κ B-Dependent Expression of Cell Adhesion Molecules. The American Journal of Chinese Medicine. 2021;49(03):737-51.

[38] Al-Amin M, Rahiman SS, Khairuddean M, Salhimi SM. (R)-(−)-Xanthorrhizol Inhibits the Migration and Invasion of Triple-Negative Breast Cancer Cells by Suppressing Matrix Metalloproteinases via the NF-κB Signaling Pathway. Planta Medica. 2024;90(10):785-91.

[39] Kim JY, An JM, Chung WY, Park KK, Hwang JK, Kim du S. et al. Xanthorrhizol induces apoptosis through ROS-mediated MAPK activation in human oral squamous cell carcinoma cells and inhibits DMBA-induced oral carcinogenesis in hamsters. Phytother Res. 2013;27(4):493–8.

[40] Lee SK, Hong CH, Huh SK, Kim SS, Oh OJ, Min HY, Park KK, Chung WY, Hwang JK. Suppressive effect of natural sesquiterpenoids on inducible cyclooxygenase (COX-2) and nitric oxide synthase (iNOS) activity in mouse macrophage cells. Journal of environmental pathology, toxicology and oncology. 2002;21(2).

[41] Kashyap D, Garg VK, Goel N. Intrinsic and extrinsic pathways of apoptosis: Role in cancer development and prognosis. Advances in protein chemistry and structural biology. 2021;125:73-120.

[42] Feitelson MA, Arzumanyan A, Kulathinal RJ, Blain SW, Holcombe RF, Mahajna J, Marino M, Martinez-Chantar ML, Nawroth R, Sanchez-Garcia I, Sharma D, Saxena NK, Singh N, Vlachostergios PJ, Guo S, Honoki K, Fujii H, Georgakilas AG, Bilsland A, Amedei A, Niccolai E, Amin A, Ashraf SS, Boosani CS, Guha G, Ciriolo MR, Aquilano K, Chen S, Mohammed SI, Azmi AS, Bhakta D, Halicka D, Keith WN, Nowsheen S. Sustained proliferation in cancer: Mechanisms and novel therapeutic targets. Semin Cancer Biol. 2015;35 Suppl(Suppl):S25-S54.

[43] Wang Z. Regulation of Cell Cycle Progression by Growth Factor-Induced Cell Signaling. Cells. 2021;10(12):3327.

[44] Montalto FI, De Amicis F. Cyclin D1 in Cancer: A Molecular Connection for Cell Cycle Control, Adhesion and Invasion in Tumor and Stroma. Cells. 2020;9(12):2648.

[45] Saman H, Raza SS, Uddin S, Rasul K. Inducing Angiogenesis, a Key Step in Cancer Vascularization, and Treatment Approaches. Cancers (Basel). 2020;12(5):1172.

[46] Fares J, Fares MY, Khachfe HH, Salhab HA, Fares Y. Molecular principles of metastasis: a hallmark of cancer revisited. Signal transduction and targeted therapy. 2020;5(1):28.

[47] Ribatti D, Tamma R, Annese T. Epithelial-mesenchymal transition in cancer: a historical overview. Translational oncology. 2020;13(6):100773.

[48] Loh CY, Chai JY, Tang TF, Wong WF, Sethi G, Shanmugam MK, Chong PP, Looi CY. The E-Cadherin and N-Cadherin Switch in Epithelial-to-Mesenchymal Transition: Signaling, Therapeutic Implications, and Challenges. Cells. 2019;8(10):1118.

[49] Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation. Science. 2009;324(5930):1029-33.

[50] Zhao H, Wu L, Yan G, Chen Y, Zhou M, Wu Y, Li Y. Inflammation and tumor progression: signaling pathways and targeted intervention. Signal Transduct Target Ther. 2021;6(1):263.

[51] Nishida A, Andoh A. The role of inflammation in cancer: mechanisms of tumor initiation, progression, and metastasis. Cells. 2025;14(7):488.

[52] Zhang T, Ma C, Zhang Z, Zhang H, Hu H. NF-κB signaling in inflammation and cancer. MedComm (2020). 2021;2(4):618-653.

[53] Meiyanto E, Larasati YA. The Chemopreventive Activity of Indonesia Medicinal Plants Targeting on Hallmarks of Cancer. Adv Pharm Bull. 2019;9(2):219-230.

[54] Yamazaki M, Maebayashi Y, Iwase N, Kaneko T. Studies on Pharmacologically Active Principles from Indonesian Crude Drugs. I. Principle Prolonging Pentobarbital-Induced Sleeping Time from Curcuma xanthorrhiza Roxb. Chemical and pharmaceutical bulletin. 1988;36(6):2070-4.

[55] Devaraj S, Esfahani AS, Ismail S, Ramanathan S, Yam MF. Evaluation of the antinociceptive activity and acute oral toxicity of standardized ethanolic extract of the rhizome of Curcuma xanthorrhiza Roxb. Molecules. 2010;15(4):2925-34.

[56] Listyawati S. Toxicity studies of the rhizome Curcuma xanthorrhiza Roxb. and Curcuma zedoaria Roscoe on hematological and male reproduction system of mice (Mus musculus L.). Biofarmasi Journal of Natural Product Biochemistry. 2006;4(1):10-3.