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Literature Review

Pomegranate extract mechanism in inhibiting the development of oral cancer: A review

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ABSTRACT

Background: Oral cancer is one of the most aggressive and invasive cancers with high metastatic potential. Oral cancer is cancer with the 11th highest number of cases in the world. Oral cancer is treated with chemotherapy and radiotherapy. However, this therapy causes side effects in the form of damage to normal cells in the surrounding tissue. Pomegranate extract contains polyphenols which may be great for inhibiting the development of oral cancer. **Purpose:** This article presents a systematic and comprehensive review of the potential of pomegranate extract as a natural product to inhibit the development of oral cancer. **Review:** Pomegranate extract was obtained by ethanol extraction using maceration method. The main content of pomegranate is polyphenolic compounds such as punicalagin, tannins, flavonoids, and ellagic acid. This compound reduces ATP formation, shortens the subG1 phase, and increases apoptosis. At the microcellular level, pomegranate extract can inhibit the activity of MMP-2 or MMP-9 to produce anti-proliferative, anti-angiogenesis and pro-apoptotic processes of cancer cells at concentrations of 25 and 50 μg/ml. Anti-proliferative and pro-apoptotic effects are produced through mitochondrial damage mechanisms. Exposure after 72 hours can reduce oral cell viability greater than exposure after 24 hours. **Conclusion:** Pomegranate extract is likely has four mechanisms to oral cancer: inhibiting the invasion, migration and growth of oral cancer cells, increasing oral cancer cell apoptosis and regulating antioxidant genes. So that this material can be used as a candidate for oral cancer therapy.

Keywords: Pomegranate, oral cancer, pro-apoptotic, anti-proliferative, natural product

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INTRODUCTION

Oral cancer is a pathological condition of oral epithelial cells that are atypical and differentiate into malignancy and continue to metastasize, which often gives clinical conditions such as ulcers that do not heal and recur.[1] Oral cancer is one of the most aggressive and invasive types of cancer and has very high metastases with the number of cases reaching 377,000 cases and 177,000 deaths.[2] According to data released by the Ministry of Health of the Republic of Indonesia in 2019, oral cancer occupies the third-highest position in the category of cancer with the highest prevalence.[3]

Generally, the therapy given is radiotherapy and tissue excision. This therapy has several drawbacks from the patient's side, including side effects of radiation exposure caused by periodic radiotherapy treatments, a broad spectrum of treatment so that it has side effects of systemic disorders in patients such as xerostomia. Radiation exposure affects and damages healthy cells and tissues in a broad spectrum of treatments. Due to these side effects, alternative therapy with the natural product is needed because it has minimal side effects.[4] The author is interested in exploring and analyzing the potential of natural products in Indonesia to be candidates for oral cancer curative therapy.

One of the natural products is pomegranate *(Punica granatum L.)*. The pomegranate, both fruit, seed and skin showed a potential for anti-cancer. In many references it has been showing anti-cancer to prostate cancer,[5–9] breast cancer,[10,11] liver cancer,[12] colon cancer,[13,14], bladder cancer,[15] and cervix cancer.[16] In addition to considering the weaknesses of previous therapies, the selection of natural ingredients is also based on the lack of literature reviews that discuss the potential for active compounds contained in natural ingredients. So, in the future, this literature can be used as the basis for further research in the development of oral cancer therapy innovations based on natural product and herbal medicine resources. This will encourage the development of innovation through both researches and writing about the potential of natural

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ingredients that are growing rapidly in Indonesia, such as the red pomegranate *(Punica granatum L.)* as a candidate for oral cancer therapy.

REVIEW

Oral Cancer

Oral cancer is a pathological condition of oral epithelial cells that are atypical and differentiate into malignancy and continue to metastasize, which often gives clinical conditions such as ulcers that do not heal and recur.[1] According to data released by the Ministry of Health on the Infodatin page in 2019, oral cancer occupies the third highest position in the category of cancer with the highest prevalence.[3] In quantitative epidemiology, WHO explains that in the world there are 377,000 positive patients diagnosed with oral cancer and 177,000 deaths due to oral cancer.[2]

Etiology of Oral Cancer

Oral cancer can be triggered by several trigger factors. However, the causative factors of oral cancer are not known with certainty. This happens because cancer occurs due to multifactorial and complex factors. However, a number of studies state that several trigger factors can influence the occurrence of oral cancer, such as local factors, exogenous factors, and host factors. Local factors that can trigger oral cancer include poor oral hygiene index (OHI) and chronic irritation from restorations. Apart from local factors, there are several exogenous factors that can trigger malignancy in the oral cavity, including smoking habits, alcoholism behavior, betel nut behavior (consuming betel), and viral infections (e.g., Human Papillomavirus). As for the host factor, it is influenced by several things, including age, gender, immunological conditions, and genetics.[17]

Pathogenesis of Oral Cancer

Oral cancer occurs after undergoing several stages, including mild dysplasia, moderate dysplasia, severe dysplasia, carcinoma in situ, and invasive cancer. Mild dysplasia or low-grade intraepithelial lesions are characterized by precancerous neoplastic processes that may affect squamous, glandular, or transitional epithelial cells without evidence of invasion. It is characterized by the presence of mild epithelial dysplasia with an enlarged nucleus of less than 50% of the cells themselves. The next stage after mild dysplasia is moderate dysplasia. Moderate dysplasia was defined as a morphological finding indicating moderate dysplastic cellular changes and architectural changes in the epithelial cells of the oral mucosa. In moderate dysplasia, no invasion or metastasis was found.[18]

The third stage is the stage of severe dysplasia. Severe dysplastic conditions are characterized by a spectrum of changes, including augmentation of immature epithelial cells, which occupy the lower half or more of the epithelial thickness. Severe dysplastic conditions were also considered a potentially premalignant lesion, with 12% of patients subsequently developing malignancy. After the cancer cells enter the stage of severe dysplasia, the cancer cells will be able to continue to develop into the condition of carcinoma in situ. Carcinoma in situ or Ca in situ is a condition in which the cancer is only present in the cells where it started and has not spread to nearby tissues. Carcinoma in situ is an early stage of cancer and is considered non-invasive. Cancer that has entered the carcinoma in situ stage can develop into invasive cancer and has the ability to metastasize to tissues located far from the site of the original lesion.[19]

Treatment

Controlling primary cancer is the main goal of oral cancer treatment. Oral cancer treatment is generally done with chemotherapy and radiotherapy.[20] However, chemotherapy and radiotherapy cause side effects such as damage to normal cell tissue. The dose of radiation needed to kill the tumor can cause temporary or permanent side effects. Temporary side effects of the radiation dose include skin erythema, mucosal ulceration, pain, candidiasis, alopecia, dermatitis, and dysgeusia. Skin telangiectasia, xerostomia with cervical caries, permanent alopecia, oral mucosa, skin atrophy, and osteoradionecrosis are all long-term side effects. Another dangerous side effect of chemotherapy and radiotherapy is causing damage to cells, interfering with cell survival and reproduction. If there are enough cells in the organ or tissue that are damaged and do not function normally, it will have an impact on the loss of function of the organ or cell tissue.[21]

Pomegranate as Drug Natural Resource

Pomegranate *(Punica granatum L.)* is a fruit plant that can grow up to 5-8 m. This plant is thought to have originated from Iran, but has long been bred in the Mediterranean region. This plant is also found in South China and Southeast Asia. Pomegranate *(Punica granatum L.)* is one of the most abundant fruits in Southeast Asia, including Indonesia.[22] Pomegranate *(Punica granatum L.)* has been widely used as herbal medicine to prevent various diseases. Pomegranate can be used to prevent cancer, cardiovascular-related diseases, and diseases of the oral cavity.[23]

Pomegranate contains several compounds that have the potential to be used as natural products in the field of dentistry. The main compounds contained in the skin of the pomegranate include tannin acid, catechin, and gallocatechin (Figure 1).[24] Pomegranate seeds contain sufficient punicic acid. In addition, there are also other fatty acids contained such as stearic acid, linoleic acid, oleic acid, and palmitic acid, each of which has a concentration ranging from 3 to 7% (Figure 1). While the fruit of the pomegranate plant contains ellagic acid, ellagitannins, gallic acid, and punicalagin.[25] (Figure 1)

Tannins contained in pomegranate are hydrolyzed tannins consisting of 3 compounds: ellagitannins, gallotannins, hydroxy benzoic acid, and hydroxy cinnamic acid. The first compound is ellagitannin. Ellagitannin is responsible for the antioxidant activity of the pomegranate. The main ellagitannin compound in pomegranate fruit is punicalagin (2,3-hexahydroxydiphenoyl-4,6-gallagyl

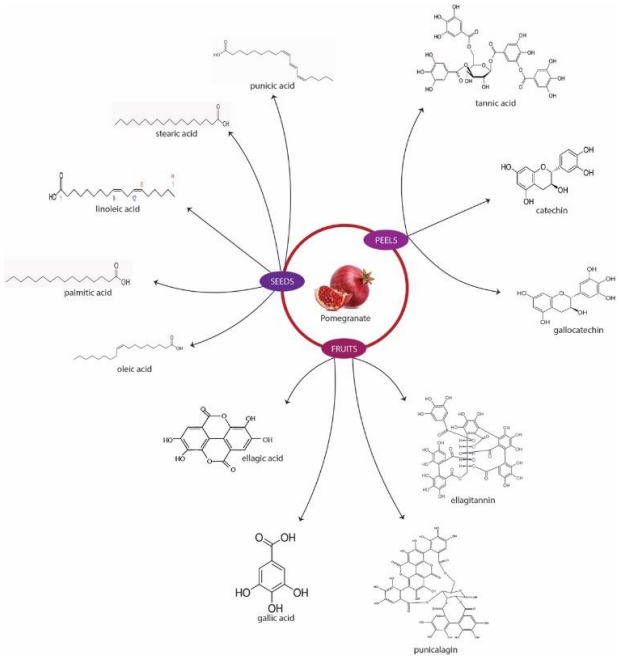

Figure 1. Graph of identification of antioxidant compounds contained in pomegranate.[23]

glucoside). In addition to punicalagin, pomegranate also contains punicalin A and B as well as several pedunculagin compounds. Gallotannin compounds can be found in several parts of the pomegranate. This compound contains a galloyl monomer and a dimer linked to a hexose. However, so far only two of the gallotannin-type compounds, namely galloyl-hexoside and mono galloyl-hexoside, have been found in pomegranates. The last of the tannins are hydroxycinnamic acid and hydroxybenzoic acid. Generally, phenolic acids can be found in pomegranates, especially cinnamic acid and benzoic acid.[23]

Pomegranate also contains citric acid and L-malic acid as the main organic acids. In addition, there are also ascorbic acid, fumaric acid, oxalic acid, kinic acid, succinic acid, and tartaric acid as additional organic acids that can be found in the leaves, fruit skin, and seed tissue of pomegranate. pomegranate. Physiologically, pomegranate is rich in unsaturated fatty acids that have good benefits.[26] The distinctive fatty acids in pomegranate are punicic acid and conjugated linoleic acid which are considered beneficial in treating various metabolic and chronic inflammatory diseases.[27]

DISCUSSION

The pomegranates have showed anti-cancer properties to various cancer. The possible mechanism to prevent and treat the oral cancer was visualized in (Figure 2). Pomegranate extract administration exhibited inhibiting the invasion, migration and growth of oral cancer cells, increasing cell apoptosis, regulating antioxidant genes and tumor growth.

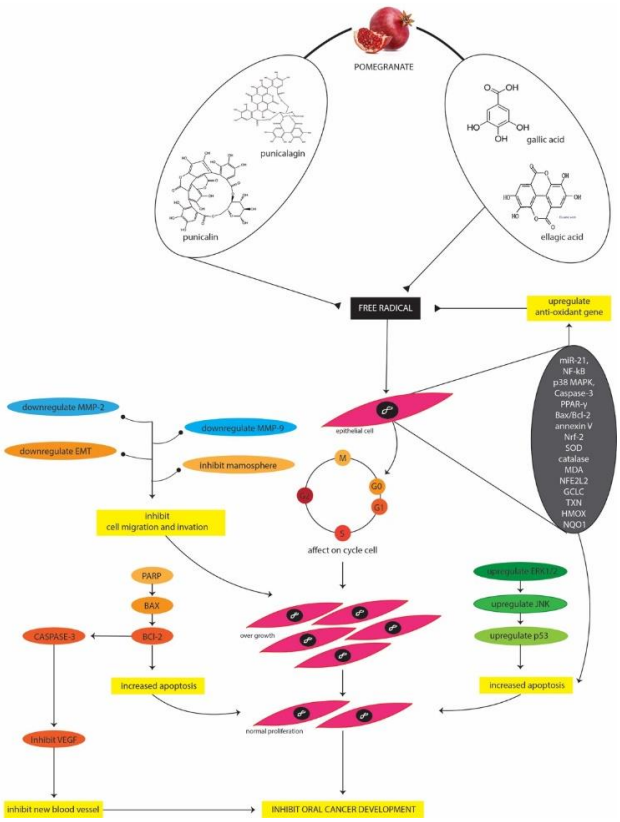

Figure 2. Concept map of the mechanism of pomegranate extract as an inhibitor of the development of oral cancer cells.

The possible mechanism of pomegranate extract in inhibiting the invasion and migration of oral cancer cells

MMP-2/-9 is an enzyme required for cell migration and invasion and has an important function in the metastasis (migration and invasion) of cancer cells. Inhibition of MMP-2/-9 by siRNA suppresses migration in retinoblastoma cells. β-mangosteen downregulates MMP-2/-9 protein expression and this way can inhibit the invasion of liver cancer cells. The same thing happened to the pomegranate. Research conducted by Peng in 2020 found that pomegranate extract suppressed MMP-2/-9 activity and expression in HSC-3 and Ca9-22 oral cancer cells. Thus, the migration of the inhibited pomegranate extract in oral cancer cells could be mediated by the inactivation of MMP-2/-9.[28] This mechanism was also found similar in gastric and ovarian cell cancer, in which the pomegranate extract inhibits the MMP-2/-9 expression and further inhibits the proliferation and migration of cancer.[29,30]

At low concentrations, pomegranate extract inhibited wound healing migratory ability, downregulated epithelial-mesenchymal transition (EMT) signaling genes, Twist mRNA expression, and inhibited mamosphere formation. Consistently, studies from Peng et al have shown that pomegranate downregulates mRNA levels of FAK, transcription factors EMT (Slug and Twist), and mesenchymal markers (vimentin and N-cadherin). In the

same study, mRNA levels of epithelial markers (E-cadherin) upregulated in HSC-3 cells showed that the EMT process was suppressed by pomegranate extract in oral cancer cells, thereby inhibiting migration and invasion of oral cancer cells. In addition, EMT-associated signalling proteins in oral cancer cells HSC-3 and Ca9-2 were downregulated by pomegranate extract.[28]

Several other studies on pomegranate extracts have focused on MAPK expression and apoptosis without considering their migratory effects. MAPK protein families (such as ERKs, JNKs and p38) regulate diverse cellular functions such as proliferation, migration, invasion, and apoptosis. Peng et al's 2020 study only focused on apoptosis and tumor inhibitory effects at high cytotoxic concentrations of the pomegranate extract without investigating its migratory effect, which was only effective at lower concentrations. Low cytotoxic concentrations (25 and 50 g/mL; cell viability of 86% and 80%, respectively) of the pomegranate extract induced ERK phosphorylation but inhibited JNK and p38 phosphorylation in HSC-3 oral cancer cells at 24 h. In addition, MAPK regulates MMP-2/-9 activation, which regulates cancer cell migration and invasion. The results study showed that the effect of pomegranate extracts upregulated ERK1/2 phosphorylation, but this was in contrast to the regulation of JNK and p38 phosphorylation. ERK1/2 inhibitors restored the pomegranate extract-induced inhibition of transwell migration and MMP-2/-9 activation. Peng et al's 2020 study concluded that pomegranate extract inhibited MMP-2/-9 activation, cell migration, and invasion through activation of ERK1/2 signaling in oral cancer cells.[28]

Possible mechanism of pomegranate extract in increasing oral cancer cell apoptosis

Increased mtDNA copy number can inhibit apoptosis. In contrast, a reduced copy number of mtDNA was shown to induce ROS generation and apoptosis in oral cancer cells. Similarly, administration of pomegranate extract after 24 and 72 h could increase oxidative stress and decrease mtDNA copy number in oral cancer cells, leading to apoptosis. Single or double-strand cleavage in mtDNA can induce apoptosis. In addition, mtDNA damage induces the detection of MitoSOX generation and subsequent apoptosis. Similarly, the treatment of 24 and 72 h pomegranate extract caused mtDNA damage, MitoSOX, and apoptosis. In addition, oxidative stress also induces oxidative DNA damage. These findings support this because pomegranate extract causes DNA double-stranded (γH2AX) damage in oral cancer cells.[31] In other research, shows that the induced ROS generation is caused by mobilizing intracellular copper ions.[32]

Changes in mitochondrial biogenesis regulate apoptosis. Biogenesis can increase mitochondrial mass and DNA copy number and is associated with apoptosis. Similarly, after administration of the pomegranate extract 24 and 72 hours, it was able to inhibit the expression of mRNA and protein for mitochondrial biogenesis of gene expression in oral cancer cells. These findings support the idea that downregulation of mitochondrial biogenesis is capable of reducing mitochondrial mass. In addition, overexpression of mitochondrial fission factor (MFF) in breast cancer cells decreases mitochondrial mass and activity. This is because pomegranate extract is able to suppress and reduce mitochondrial biogenesis and mass, it is possible that administration of pomegranate extract causes mitochondrial fusion and causes apoptosis of oral cancer cells. This warrants a detailed investigation of the role of mitochondrial fission in the delivery of pomegranate extract to oral cancer cells in the future.[31] To induce the apoptosis, in the other hands, pomegranate mediated through regulating miR-21,[33] NF-kB,[33–37] and p38 MAPK,[38] cleavings Caspase-3,[39] tumour PPAR-γ,[39] increasing the Bax/Bcl-2 ratio and the annexin V expression.[31]

The ability of pomegranate extract to regulate antioxidant genes

When the cellular pro-oxidant level is higher than the antioxidant level, oxidative stress will be generated cellularly. Antioxidant gene expression is also affected by mitochondrial damage. Late glycation end products are reported to inhibit cellular antioxidant systems and trigger oxidative stress.[28] The pomegranates regulated oxidative stress,[40] through the regulation of antioxidant properties by an increase in Nrf-2,[34,37] superoxide dismutase (SOD) and catalase activities, and decrease a MDA.[39]

This is similar to a study conducted by Peng et al in 2021 which showed that mRNA expression for several antioxidant genes including NFE2L2, GCLC, TXN, CAT, SOD1, HMOX1, and NQO1 was downregulated at 24 hours after administration of pomegranate extract against three types of oral cancer cell test groups namely Ca9-22, HSC-3, and OC-2 cells. In addition, protein expression for this antioxidant gene was also downregulated at 72 h post-administration of pomegranate extract for oral cancer cells (HSC-3 and OC-2) but had a slight downregulation effect for the oral cancer cell Ca9-22 assay group.[28]

These results suggest that mRNA and protein expression for antioxidant signaling may be differentially regulated between different test oral cancer cell types. Under this differential regulation mode, oxidative stress such as MitoMP depletion and MitoSOX generation were upregulated at 12, 24, and 72 h post administration of the pomegranate extract against three assay oral cancer cells Ca9-22, HSC-3, and OC-2 cells. Therefore, the antioxidant signaling pathway plays a vital function in the oxidative stress induced by the pomegranate extract.[28]

Possible mechanism of pomegranate extract as an inhibitor of oral cancer cell growth

Pomegranate extract is one of the fruits that are rich in antioxidant compounds. According to data in a journal written by Peng, et al in 2021, it showed that pomegranate extract had antiproliferative activity on Ca9-22, HSC-3, and OC-2 test cancer cells, respectively at IC50 doses of 80.53, 100.34, and 108.12 g/mL when the ATP assay was performed after 24 hours of administration of the pomegranate extract.[31]

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Not only works as an antiproliferative against all target cells, but pomegranate extract also has antiproliferative selectivity only for cancer cells. The selective antiproliferative ability of pomegranate extract has been well observed in several existing studies. For example, normal human prostate epithelial PrEC cells showed no cytotoxicity (95% viability) to the pomegranate extract. In the MTT test on objects that have been given pomegranate extract for 72 hours, it was found that the pomegranate extract with levels of 50-150 g/mL showed anti-proliferation against lung cancer cells with 53% viability but no cytotoxic effect on normal bronchial epithelial cells with 90% viability. In another study, pomegranate extract showed antiproliferation and apoptosis in prostate cancer cells but no cytotoxicity in normal prostate epithelial cells. The other inhibition mechanism of cancer cell growth was inhibiting the VEGF expression,[41] EMT,[42,43] and metastasis.[42] Compounds that act in pomegranate extract are punicalagin and ellagic acid, the two main components of this pomegranate extract work by inducing apoptosis of colon cancer cells without affecting normal intestinal cells. Therefore, pomegranate extract and other natural products derived from pomegranate are able to have antiproliferative properties that are selective against some cancer cells and do not show side effects on normal oral cavity cells.[31]

CONCLUSION

The pomegranate extract possibly has four mechanisms to oral cancer: inhibiting the invasion, migration and growth of oral cancer cells, increasing oral cancer cell apoptosis and regulating antioxidant genes.

Suggestion

Based on the literature review analysis that has been carried out, it is recommended that more detailed research on the antimetastatic properties of pomegranate extracts at low cytotoxic concentrations is recommended.

REFERENCES

1. Budhy TI. Mengapa Terjadi Kanker. Edisi Kedua/Patobiologi. Surabaya: Airlangga Press; 2019. 1–27 p.
2. WHO. Oral Squamous Cell Carcinoma: Worldwide Prevalence. [Internet]. Available from: https://www.who.int/news-room/fact-sheets/detail/oral-health.
3. Indonesia KKR. Situasi Kesehatan Gigi dan Mulut 2019 [Internet]. Available from: https://www.kemkes.go.id/article/view/20030900005/situasi-kesehatan-gigi-dan-mulut-2019.html.
4. Gharat SA, Momin M, Bhavsar C. Oral Squamous Cell Carcinoma: Current Treatment Strategies and Nanotechnology-Based Approaches for Prevention and Therapy. Crit Rev Ther Drug Carrier Syst. 2016;33(4):363–400.
5. Grammatikopoulou MG, Gkiouras K, Papageorgiou ST, Myrogiannis I, Mykoniatis I, Papamitsou T, et al. Dietary Factors and Supplements Influencing Prostate Specific-Antigen (PSA) Concentrations in Men with Prostate Cancer and Increased Cancer Risk: An Evidence Analysis Review Based on Randomized Controlled Trials. Nutrients. 2020 Sep 29;12(10):2985.
6. Cicero AFG, Allkanjari O, Busetto GM, Cai T, Larganà G, Magri V, et al. Nutraceutical treatment and prevention of benign prostatic hyperplasia and prostate cancer. Arch Ital di Urol Androl organo Uff [di] Soc Ital di Ecogr Urol e Nefrol. 2019 Oct 2;91(3).
7. Zuniga KB, Chan JM, Ryan CJ, Kenfield SA. Diet and lifestyle considerations for patients with prostate cancer. Urol Oncol. 2020 Mar;38(3):105–17.
8. Wang L, Martins-Green M. Pomegranate and its components as alternative treatment for prostate cancer. Int J Mol Sci. 2014 Aug 25;15(9):14949–66.
9. Paller CJ, Pantuck A, Carducci MA. A review of pomegranate in prostate cancer. Prostate Cancer Prostatic Dis. 2017 Sep;20(3):265–70.
10. Li Y, Li S, Meng X, Gan R-Y, Zhang J-J, Li H-B. Dietary Natural Products for Prevention and Treatment of Breast Cancer. Nutrients. 2017 Jul 8;9(7):728.
11. Sturgeon SR, Ronnenberg AG. Pomegranate and breast cancer: possible mechanisms of prevention. Nutr Rev. 2010 Feb;68(2):122–8.
12. Zhou Y, Li Y, Zhou T, Zheng J, Li S, Li H-B. Dietary Natural Products for Prevention and Treatment of Liver Cancer. Nutrients. 2016 Mar 10;8(3):156.
13. Aiello P, Sharghi M, Mansourkhani SM, Ardekan AP, Jouybari L, Daraei N, et al. Medicinal Plants in the Prevention and Treatment of Colon Cancer. Oxid Med Cell Longev. 2019;2019:2075614.
14. Jaganathan SK, Vellayappan MV, Narasimhan G, Supriyanto E. Role of pomegranate and citrus fruit juices in colon cancer prevention. World J Gastroenterol. 2014 Apr 28;20(16):4618–25.
15. Philippou Y, Hadjipavlou M, Khan S, Rane A. Complementary and alternative medicine (CAM) in prostate and bladder cancer. BJU Int. 2013 Dec;112(8):1073–9.
16. Teniente SL, Flores-Gallegos AC, Esparza-González SC, Campos-Múzquiz LG, Nery-Flores SD, Rodríguez-Herrera R. Anticancer Effect of Pomegranate Peel Polyphenols against Cervical Cancer. Antioxidants. 2023 Jan 5;12(1):127.
17. Sirait AM. Faktor risiko tumor/kanker rongga mulut dan tenggorokan di Indonesia. Media Litbangkes. 2013;23(3):122–9.
18. Hrelec C. Management of Laryngeal Dysplasia and Early Invasive Cancer. Curr Treat Options Oncol. 2021 Aug 23;22(10):90.
19. Gale N, Blagus R, El-Mofty SK, Helliwell T, Prasad ML, Sandison A, et al. Evaluation of a new grading system for laryngeal squamous intraepithelial lesions--a proposed unified classification. Histopathology. 2014 Oct;65(4):456–64.
20. Wibowo IS, Priyanto W, Hardianto A. Karakteristik Karsinoma Sel Skuamosa Rongga Mulut di Rsup DR. Hasan Sadikin Bandung Periode Januari-Desember 2019. J Kedokt dan Kesehat Publ Ilm Fak Kedokt Univ Sriwij. 2022 Feb 17;9(1):97–102.
21. Zraik IM, Heß-Busch Y. [Management of chemotherapy side effects and their long-term sequelae]. Urologe A. 2021 Jul;60(7):862–71.
22. Hardana H, Warganegara E. Ekstrak Buah Delima Sebagai Antibiotik Pengobatan Infeksi MRSA. Majority. 2015;4(9):83–7.
23. Vučić V, Grabež M, Trchounian A, Arsić A. Composition and

Potential Health Benefits of Pomegranate: A Review. Curr Pharm Des. 2019 Aug 23;25(16):1817–27.
24. Akhavan H, Barzegar M, Weidlich H, Zimmermann BF. Phenolic Compounds and Antioxidant Activity of Juices from Ten Iranian Pomegranate Cultivars Depend on Extraction. J Chem. 2015;2015:1–7.
25. Wong TL, Strandberg KR, Croley CR, Fraser SE, Nagulapalli Venkata KC, Fimognari C, et al. Pomegranate bioactive constituents target multiple oncogenic and oncosuppressive signaling for cancer prevention and intervention. Semin Cancer Biol. 2021 Aug;73:265–93.
26. Rafiq Z, Narasimhan S, Vennila R, Vaidyanathan R. Punigratane, a novel pyrrolidine alkaloid from Punica granatum rind with putative efflux inhibition activity. Nat Prod Res. 2016 Dec;30(23):2682–7.
27. Aruna P, Venkataramanamma D, Singh AK, Singh RP. Health Benefits of Punicic Acid: A Review. Compr Rev food Sci food Saf. 2016 Jan;15(1):16–27.
28. Peng S-Y, Hsiao C-C, Lan T-H, Yen C-Y, Farooqi AA, Cheng C-M, et al. Pomegranate extract inhibits migration and invasion of oral cancer cells by downregulating matrix metalloproteinase-2/9 and epithelial-mesenchymal transition. Environ Toxicol. 2020 Jun;35(6):673–82.
29. Cheshomi H, Bahrami AR, Rafatpanah H, Matin MM. The effects of ellagic acid and other pomegranate (Punica granatum L.) derivatives on human gastric cancer AGS cells. Hum Exp Toxicol. 2022;41:9603271211064534.
30. Liu H, Zeng Z, Wang S, Li T, Mastriani E, Li Q-H, et al. Main components of pomegranate, ellagic acid and luteolin, inhibit metastasis of ovarian cancer by down-regulating MMP2 and MMP9. Cancer Biol Ther. 2017 Dec 2; 18(12):990–9.
31. Peng S-Y, Lin L-C, Chen S-R, Farooqi AA, Cheng Y-B, Tang J-Y, et al. Pomegranate Extract (POMx) Induces Mitochondrial Dysfunction and Apoptosis of Oral Cancer Cells. Antioxidants (Basel, Switzerland). 2021 Jul 13;10(7):1117.
32. Farhan M, Rizvi A, Ali F, Ahmad A, Aatif M, Malik A, et al. Pomegranate juice anthocyanidins induce cell death in human cancer cells by mobilizing intracellular copper ions and producing reactive oxygen species. Front Oncol. 2022;12:998346.
33. Hussein AM, El-Beih NM, Swellam M, El-Hussieny EA. Pomegranate juice and punicalagin-mediated chemoprevention of hepatocellular carcinogenesis via regulating miR-21 and NF-κB-p65 in a rat model. Cancer Cell Int. 2022 Nov 2;22(1):333.
34. Mukherjee S, Ghosh S, Choudhury S, Gupta P, Adhikary A, Chattopadhyay S. Pomegranate Polyphenols Attenuate Inflammation and Hepatic Damage in Tumor-Bearing Mice: Crucial Role of NF-κB and the Nrf2/GSH Axis. J Nutr Biochem. 2021 Nov;97:108812.
35. Wang XZ, Zhang SF, Yang ZH, Ye ZW, Liu J. Punicalagin suppresses osteosarcoma growth and metastasis by regulating NF-κB signaling. J Biol Regul Homeost Agents. 2020;34(5):1699–708.
36. Huang T, Zhang X, Wang H. Punicalagin inhibited proliferation, invasion and angiogenesis of osteosarcoma through suppression of NF-κB signaling. Mol Med Rep. 2020 Sep;22(3):2386–94.
37. Mandal A, Bhatia D, Bishayee A. Anti-Inflammatory Mechanism Involved in Pomegranate-Mediated Prevention of Breast Cancer: the Role of NF-κB and Nrf2 Signaling Pathways. Nutrients. 2017 Apr 28;9(5):436.
38. Li H-M, Kouye O, Yang D-S, Zhang Y-Q, Ruan J-Y, Han L-F, et al. Polyphenols from the Peels of Punica granatum L. and Their Bioactivity of Suppressing Lipopolysaccharide-Stimulated Inflammatory Cytokines and Mediators in RAW 264.7 Cells via Activating p38 MAPK and NF-κB Signaling Pathways. Molecules. 2022 Jul 20;27(14):4622.
39. Elbakry MMM, ElBakary NM, Hagag SA, Hemida EHA. Pomegranate Peel Extract Sensitizes Hepatocellular Carcinoma Cells to Ionizing Radiation, Induces Apoptosis and Inhibits MAPK, JAK/STAT3, β-Catenin/ NOTCH, and SOCS3 Signaling. Integr Cancer Ther. 2023;22:15347354221151020.
40. Lorzadeh E, Heidary Z, Mohammadi M, Nadjarzadeh A, Ramezani-Jolfaie N, Salehi-Abargouei A. Does pomegranate consumption improve oxidative stress? A systematic review and meta-analysis of randomized controlled clinical trials. Clin Nutr ESPEN. 2022 Feb;47:117–27.
41. Morsy RAA, Abbass EA, Hager EAA, Farid MH, Ellithy MM, Azmy A. Assessment of Anti-carcinogenic Effect of Pomegranate in Oral Squamous Cell Carcinoma (Pre-clinical Study). Pakistan J Biol Sci PJBS. 2019 Jan;22(12):580–4.
42. Bagheri M, Fazli M, Saeednia S, Kor A, Ahmadiankia N. Pomegranate peel extract inhibits expression of β-catenin, epithelial mesenchymal transition, and metastasis in triple negative breast cancer cells. Cell Mol Biol (Noisy-le-grand). 2018 May 30;64(7):86–91.
43. Nallanthighal S, Elmaliki KM, Reliene R. Pomegranate Extract Alters Breast Cancer Stem Cell Properties in Association with Inhibition of Epithelial-to-Mesenchymal Transition. Nutr Cancer. 2017 Oct;69(7):1088–98.

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