REVIEW ARTICLE

Potential of *Moringa Oleifera* as Anti-Cancer Agents in Oral Cancer: A Review

Deddy Adam[1,2], Ifuling Audrien Yansen[1], Fahria[1], Theresia Indah Budhy[3,4], *Alexander Patera Nugraha[5]

[1] Graduated Student of Immunology, Postgraduate School, Universitas Airlangga, 60115 Surabaya, Indonesia
[2] Department of Medical Laboratory Technology, Politeknik Kesehatan Kementerian Kesehatan Surabaya, 60296, Surabaya, Indonesia
[3] Department of Immunology, Postsgraduate School, Universitas Airlangga, 60115 Surabaya, Indonesia
[4] Department of Oral and Maxilofacial Pathology, Faculty of Dental Medicine, Universitas Airlangga, 60132 Surabaya, Indonesia
[5] Department of Orthodontic, Faculty of Dental Medicine, Universitas Airlangga, 60132 Surabaya, Indonesia

ABSTRACT

Cancer is a non-communicable disease that has a high death rate. The medical community's focus on cancer treatment options continues to this day. Chemotherapy, percutaneous ablation, surgical treatment, and resection are all treatment approaches that are still being developed. Apart from the benefits of this strategy, the researcher searched electronic databases for various research journal articles. Sciencedirect, CINAHL, Pub Med, Elsevier (SCOPUS), and Pro-Quest were among the electronic databases used. *Moringa oleifera*, Anti-Cancer, and Oral Cancer are the keywords utilized. Researchers independently scanned the relevancy of all references by title and abstract, focusing on the recent ten years. The journals were then categorized based on inclusion and exclusion criteria, such as IC1= English-language journals, IC2 = articles published between 2012 and 2022, IC3 = quantitative research types, and IC4 = non-duplicate journals from Sciencedirect, CINAHL, Pub Med, Elsevier (SCOPUS), and Pro Quest. Following the adjustments based on IC1-IC4, *Moringa oleifera* contains glucosinolates, bioactive -4-(-L-rhamnosyloxy) benzyl isothiocyanate, -sitosterol-3-O-D-glucopyranoside, nizimicin, and ITC type MIC-1, which can prevent cancer cell expansion and proliferation, slow carcinogenesis, to cause apoptosis, and inhibit tumor angiogenesis. A review of the literature that has been found shows *Moringa oleifera* can be used to cure cancer, especially oral cancer

Keywords: *Moringa oleifera*, Anti-cancer, Oral cancer

Corresponding Author:
Alexander Patera Nugraha
Email: alexander.patera.nugraha@fkg.unair.ac.id
Tel: +62315041536

INTRODUCTION

Cancer is a disease with a high mortality rate, which is caused by abnormal and uncontrolled cell growth. Cancer growth can damage surrounding cells. The spread of cancer can harm the cells around it. As stated by the World Health Organization (WHO), there were 19.3 million new cancer diagnoses in 2020, with a death rate of 10 million (1). The prevalence of Non-Communicable Diseases, such as cancer, stroke, chronic renal disease, diabetes mellitus, and hypertension, has increased in Indonesia, according to the 2018 Basic Health Research. The prevalence of cancer has risen from 1.4 percent in 2013 to 1.8 percent in 2018 (2).

Oral cancer is cancer with the highest fatality rate of all cancers. Oral squamous cell carcinoma (OSCC) accounts for approximately 95% of all oral malignancies. Oral cancer now affects those under the age of 40, it is present in men three times as often as it is in women. Oral cavity tumors were the most prevalent tumor site (35.37 percent), and oral squamous cell carcinoma was the most common histologic type (96.7 percent of cases). Smoking and alcohol intake, viral and bacterial infections, dietary inadequacies, denture irritation, and immunosuppression are all risk factors for oral squamous cell carcinoma. The most significant risk factor for mouth cancer is smoking (3).

Chemotherapy, percutaneous ablation, surgical treatment, and resection are all frequent cancer treatment approaches (4–7). Chemotherapy treatment for cancer is a viable choice for many cancer patients in Indonesia. However, cancer treatment with chemotherapeutic medications frequently fails due to anticancer treatments' limited selectivity. As a result, efforts must be made to find safe and selective anticancer medications for the treatment and prevention of cancer, particularly those derived from plants that are therapeutic (8).

Moringa oleifera is a botanical with several therapeutic uses, including cancer treatment. The three bioactive components -4-(-L-rhamnosyloxy) benzyl isothiocyanate, -sitosterol-3-O-D-glucopyranoside, and nizimicin have been linked to the anticancer activity

of *Moringa oleifera* leaves, which suppress cancer cell development and proliferation (9). *Moringa oleifera* extract contains glucosinolates, which have been shown to induce cancer cell death. To maintain a normal condition, apoptosis (programmed cell death) is essential for tissue formation, damage cell elimination, and balance between cell death and cell proliferation. Cancer can result from a disruption of this equilibrium (10).

Moringa leaves contain glucosinolates, which create ITC type MIC-1. MIC-1 has one biological characteristic, which is anti-inflammatory. Inflammation is the body's protective response many different internal and external factors originating from natural, artificial, or synthetic sources, such as physical pressure, radiation, soaring temperatures, stimulation, infections, and metabolic stress, and there is mounting indication of persistent inflammation contributes to cancer. Activated macrophages are hypothesized to exacerbate chronic inflammation by producing excessive amounts of cytokines, chemokines, lysozymes, proteases, and growth factors, which are inflammatory mediators. The failure of numerous transcription factors to limit the incident and progression of inflammation can be caused by MIC-1. It demonstrates the anti-cancer potential of MIC-1 (11).

Moringa oleifera has also been shown to have anti-cancer properties by suppressing migration, expansion, and cell proliferation via altering various cell signaling pathways. *Moringa oleifera* extract has a significant anti-cancer effect on melanoma cells in vitro involving mitochondrial-dependent caspase-mediated enzymes and caspase-independent apoptotic pathways, according to studies demonstrating *Moringa oleifera* extract has a substantial anti-cancer effect on melanoma cells cultured in vitro using mitochondrial-dependent caspase-mediated enzymes and caspase-independent apoptotic *Moringa oleifera* also have the capacity to suppress tumor growth while maintaining normal body physiology and function, making them a viable cancer treatment option (11).

Moringa oleifera's medicinal potential has also been investigated in cancer cachexia. In experimental mice, *Moringa oleifera* boosted ATPase activity, hinting that it can help with muscle degeneration during cancer cachexia. Furthermore, the antioxidant capabilities of *Moringa oleifera* have been discovered, reducing oxidative stress while a cancer cachexia is occurring. However, these features have only been established in experimental animals, and human trials are needed before solid evidence of efficacy for *Moringa oleifera*'s usage in cancer cachexia can be achieved (9). This extract can also act as a tumor suppressor gene inducer during cancer treatment in some situations. Not a single moringa seed extract found to have an antiproliferative effect on cancer cells, however, Moringa leaf and bark extracts have (9).

Moringa leaf extract's in vitro effects on numerous cell lines for cancer have been studied. *Moringa oleifera* are effective against esophageal cancer, hepatocellular carcinoma, and colorectal cancer. Because of the action of *Moringa oleifera* extract on various cancers, it is critical to look into the impact of this extract against oral cancer cells.

METHODS

In this study, the method is a Literature Review. Researchers used electronic databases to look for several academic journal articles. Sciencedirect, CINAHL, Pub Med, Elsevier (SCOPUS), and Pro-Quest were among the electronic databases used. *Moringa oleifera*, Anti-Cancer, and Oral Cancer are the keywords utilized. Sciencedirect 10 journals, Elsevier (SCOPUS) 4 journals, CINAHL 5 journals, and Pubmed 5 journals returned search results. Researchers independently scanned the relevancy of all references by title and abstract, focusing on the recent ten years. The journals were then categorized based on inclusion and exclusion criteria, such as IC1 = English-language journals, IC2 = articles published between 2011 and 2022, IC3 = quantitative research types, and IC4 = non-duplicate journals from Sciencedirect, CINAHL, Pub Med, Elsevier (SCOPUS), and Pro Quest. The remaining articles are 14 after adjusting depending on IC1-IC4. The reviewer next performs IC5 in the form of selecting articles based on the article title and abstract's suitability for this literature review, which is to investigate the role of *Moringa oleifera* as an anticancer. As a result, 5 journals were chosen to be studied. Figure 1 shows the workflow for selecting literature reviews.

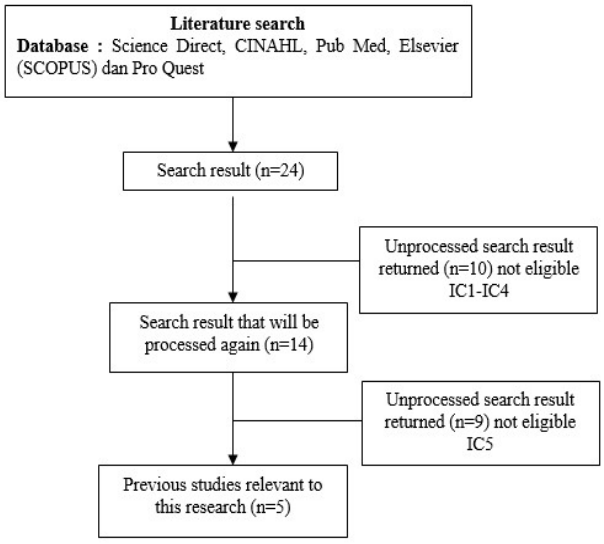

Fig. 1: Flowchart of literature review selection

RESULT AND DISCUSSION

The role of *Moringa oleifera* as an anticancer that has been found is described in table I, where *Moringa oleifera* has several specific ingredients that function to inhibit cancer growth. Oral cancer is a malignancy that develops in and around the mouth; squamous cell carcinomas emerging from the oral epithelium account for more than 90% of all lesions. Squamous carcinoma of the oral cavity (oral cancer) should be distinguished from oropharyngeal carcinoma. Human papillomavirus (HPV) infection is linked to oropharyngeal cancer, which has a variety of clinical and histologic characteristics. Oral cancer is linked to the consumption of tobacco and alcohol. Oral cancer can be found on the front tongue's lips, gingiva, mouth floor, palate, and other parts of the mouth (12).

Table 1: *Moringa oleifera* content as anti-cancer

No	*Content*	*Function*
1	Glukosinolat (10,13)	Slows carcinogenesis and promotes detoxification from carcinogens, anti-inflammatory, anti-tumor, apoptosis, and tumor angiogenesis inhibition
2	Three bioactive components : ✓ 4-(α-L-rhamnosyloxy) benzil isothiocyanate ✓ Sitosterol-3-O-β-D-glucopyranoside ✓ Nizimicin(9)	preventing the development of cancer cells and proliferation
3	ITC type MIC-1 (11)	MIC-1 can lead to the failure of numerous transcription factors to prevent the onset and development of inflammation when they are activated
4	Quinic acid, octadecanoic acid, hexadecanoic acid (palmitic acid), α-tocopherol (vitamin-E),and G-sitosterol(14)	Potentially inhibits tumor development As a cancer therapeutic drug, without altering normal bodily physiology and function

The migration of epithelial cells through the basement membrane into the superficial connective tissue is the defining criterion for diagnosing oral cancer. Multiple tiny epithelia are frequently invaded first, followed by submucosal infiltration and malignant cells. This invasion process results in clinical indicators of cancer, such as a hardened (indurated) lesion that is fixed to the underlying tissue. All of the squamous cells can be seen in the surface epithelium under a microscope. It can also rise above the mucosal surface, resulting in an exophytic component in many cases (12).

Moringa oleifera contain anti-cancer properties and could be used to treat a variety of cancers. Acute lymphoblastic leukemia, myeloid leukemia, and hepatocellular cancer cell viability are all inhibited by moringa leaf extract. Niazimicin, -sitosterol-3-o-d-glucopyranoside, and 4-(-l-rhamnosyloxy) benzyl isothiocyanate were found to be the bioactive substances that cause the inhibition. *Moringa oleifera* were found to suppress pancreatic cancer's increase cells in a study by Berkovich et al. (2013) The concentration of cells in the sub-g1 phase is caused by cell cycle targets. *Moringa oleifera* also reduces the expression of the proteins ικbα, p-ibκα, and p65, which inhibits the NFκB pathway. It promotes cytotoxicity in pancreatic cancer cells in a synergistic manner with cisplatin (13).

Sadek et al., (2017) found that *Moringa oleifera* prevented liver cancer in mice that had been caused by diethyl nitrosamine (15). Madi et al., (2016) studied the extract of *Moringa oleifera*, which has antiproliferative effects on lung cancer cells as a result of their findings. The induction of p53, caspases, and parp-1 cleavage was induced by *Moringa oleifera* extract, which elevated reactive oxygen species. Apoptosis occurs in cancer cell lines as a result of this. *Moringa oleifera* extract also protects against oxidative stress and fragmentation of DNA. Furthermore, extracts increased the expression of apoptotic markers, which cause cancer cell death. *Moringa oleifera* leaf extract increases ROS production, caspase-9, -3/7 activity, and MAPK activation in human melanoma cells, causing mitochondrial-mediated apoptosis. *Moringa oleifera* contains glucosinolates, which are beneficial against cancer by triggering apoptosis (16).

Anticancer medicines that target how cancer cells work are needed because cancer cells increase quickly. *Moringa oleifera* have been proven to have a variety of functions, including the ability to target several proteins and prevent the growth of cancer cells. *Moringa oleifera* have the potential to be used in the development of new cancer-fighting alternatives and complementary therapies. The leaves and bark have anticancer properties. On the cancer cell lines hct-8 and mda-mb-231, it had an antiproliferative impact. The seed extract, on the other hand, is ineffective. The g2/m phase cell cycle is terminated, and apoptosis ensues. Bioactive substances like d-alose, hexadecanoic acid ethyl ester, eugenol, and isopropyl isothiocyanate are thought to have anticancer properties. This is critical since the bioactive chemicals found contain sugar moieties, aromatic rings, and long-chain hydrocarbons. As a result, the potential of Moringa leaves in the creation of novel medications for cancer treatment may be recognized (13)

CONCLUSION

Moringa oleifera is a plant that contains glucosinolates, bioactive -4-(-L-rhamnosyloxy) benzyl isothiocyanate,

-sitosterol-3-O—D-glucopyranoside, and nizimicin and ITC MIC-types, as well as glucosinolates, anti-inflammatory, anti-tumor cell proliferation, induce apoptosis and inhibit tumor angiogenesis. *Moringa oleifera* can be utilized to cure cancer, especially oral cancer, because of this performance.

ACKNOWLEDGEMENTS

The authors would like to thank those who are in the master's program of immunology, my family, and the entire community of Universitas Airlangga who have contributed to helping me complete this research.

REFERENCES

1. Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2021: 71(3): 209-249.doi: 10.3322/caac.21660.
2. Kemenkes RI. Hasil utama RISKESDAS 2018. Jakarta Kemenkes RI. 2018. availabel from: https://www.litbang.kemkes.go.id/hasil-utama-riskesdas-2018/
3. Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., and Jemal, A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2018: 68(6): 394-424. doi: 10.3322/caac.21492
4. Zhao, C.Y., Cheng, R., Yang, Z. and Tian, Z.M. Nanotechnology for cancer therapy based on chemotherapy. Molecules. 2018: 23(4): 826. doi: 10.3390/molecules23040826.
5. Solbiati, L., Ahmed, M., Cova, L., Ierace, T., Brioschi, M. and Goldberg, S.N., 2012. Small liver colorectal metastases treated with percutaneous radiofrequency ablation: local response rate and long-term survival with up to 10-year follow-up. Radiology. 2012: 265(3): 958-968. doi: 10.1148/radiol.12111851.
6. Abdalla, E.K., Vauthey, J.N., Ellis, L.M., Ellis, V., Pollock, R., Broglio, K.R., Hess, K. and Curley, S.A. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. Annals of surgery. 2004: 239(6): p.818. doi: 10.1097/01.sla.0000128305.90650.71.
7. Petre, E.N. and Sofocleous, C. Thermal ablation in the management of colorectal cancer patients with oligometastatic liver disease. Visceral medicine. 2017: 33(1): 62-68. doi: 10.1159/000454697.
8. Apriani, R., Gaffar, S. and Herlina, T. Aktivitas Sitotoksik Fraksi Etil Asetat Daun Kelor (*Moringa Oleifera*) dan pengaruhnya Terhadap Induksi Apoptosis Pada Sel Kanker Payudara T47D. Jurnal Ilmiah Farmako Bahari. 2019: 10(1): 9-16. doi: 10.52434/jfb.v10i1.509.
9. Yadav, N.R., Jain, M., Sharma, A., Aggarwal, A., Pahuja, M., Mehta, A., Rawal, A. and Jain, V. 2021. Role of a Miracle Tree (*Moringa oleifera*) in Healthcare. Journal of Evolution of Medical and Dental Sciences. 2021: 10(21): 1628-1633. doi: 10.14260/jemds/2021/338.
10. Sreelatha, S., Jeyachitra, A. and Padma, P.R. Antiproliferation and induction of apoptosis by *Moringa oleifera* leaf extract on human cancer cells. Food and Chemical Toxicology. 2011: 49(6): 1270-1275. doi: 10.1016/j.fct.2011.03.006.
11. Wu, Y.Y., Xu, Y.M. and Lau, A.T. Anti-cancer and medicinal potentials of Moringa isothiocyanate. Molecules. 2021: 26(24): p.7512. doi: 10.3390/molecules26247512.
12. Speight, P.M. and Farthing, P.M.. The pathology of oral cancer. British dental journal. 2018: 225(9): 841-847. Available from: https://www.nature.com/articles/sj.bdj.2018.926.
13. Tiloke, C., Anand, K., Gengan, R.M. and Chuturgoon, A.A. *Moringa oleifera* and their phytonanoparticles: Potential antiproliferative agents against cancer. Biomedicine & Pharmacotherapy. 2018: 108: 457-466. doi: 10.1016/j.biopha.2018.09.060.
14. Barhoi, D., Upadhaya, P., Barbhuiya, S.N., Giri, A. and Giri, S. Aqueous extract of *Moringa oleifera* exhibit potential anticancer activity and can be used as a possible cancer therapeutic agent: a study involving in vitro and in vivo approach. Journal of the American College of Nutrition. 2021: 40(1): 70-85. doi: 10.1080/07315724.2020.1735572.
15. Sadek, K.M., Abouzed, T.K., Abouelkhair, R. and Nasr, S. The chemo-prophylactic efficacy of an ethanol *Moringa oleifera* leaf extract against hepatocellular carcinoma in rats. Pharmaceutical biology. 2017: 55(1): 1458-1466. doi: 10.1080/13880209.2017.1306713.
16. Madi, N., Dany, M., Abdoun, S. and Usta, J. *Moringa oleifera*'s nutritious aqueous leaf extract has anticancerous effects by compromising mitochondrial viability in an ROS-dependent manner. Journal of the American College of Nutrition. 2016: 35(7): 604-613. doi: 10.1080/07315724.2015.1080128.