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ARTICLE REVIEW: UTILIZATION OF CURCUMIN AS AN ANTI-CANCER AGENT

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ABSTRACT

The uncontrolled growth of abnormal cells in one area of the body can spread to other tissues and create more cancer cells, a disease known as cancer. Malignant cancer cells have the potential to become fatal. After cardiovascular disease, cancer is the second most common cause of mortality. Numerous cancer types exist, including stomach, liver, colorectal, lung, breast, and cervical cancers. More than 70% of cancer-related deaths occur in low- and middle-income nations, and the number of cancer-related deaths is predicted to rise steadily, hitting 11.5 million by 2030. Some of the resources utilized to look up information on curcumin's application as an anticancer agent are PubMed, Science Direct, and Google Scholar. Most of the articles that were used were published between 2013 and 2023, or within the last ten years. These journals were found using the following keywords: "Curcumin," "Cancer," "Curcumin as an Anticancer," and "Utilization of Curcumin as an Anticancer Agent." Scholars from many nations have conducted comparable investigations on the application of curcumin as an anticancer agent. Furthermore, it has been established that curcumin directly inhibits cancer cells when used as an anticancer drug. This suggests that curcumin does have anticancer properties.

Keywords: Curcumin, Cancer, Curcumin as an Anticancer agent

INTRODUCTION

The societal paradigm of diseases has evolved as a result of dietary and lifestyle changes. With its tropical environment and dual burden of infectious and non-infectious diseases such as cancer and degenerative disorders, Indonesia is a prime example of this paradigm shift. In cancer, aberrant cells proliferate uncontrollably in specific body regions and have the ability to invade other tissues, resulting in the formation of additional cancer cells. Malignant cancer cells have the potential to become fatal. All cell types in the human body can develop into cancer cells. Through connective tissue, blood, nerves, and tissue-supporting organs in the body, cancer cells can spread to other organs. The bodily portion that is impacted faces growth-related challenges (Director General of Disease Control and Environmental Health, 2009).

In addition, after cardiovascular illness, cancer is the second most common cause of mortality. There are numerous types of cancer, some of which are stomach, liver, colorectal, lung, breast, and cervical cancers. According to estimates, 11.5 million deaths from cancer would occur in low- to middle-income countries by 2030, accounting for more than 70% of all cancer deaths. The primary causes of cancer include alcohol consumption, smoking, poor diet (not eating enough fruits and vegetables), physical inactivity, chronic helicobacter pylori infection, hepatitis B and C viruses, and occupational environmental risks related to radiation and ionization (Warganegara & Nur, 2016).

According to a 2012 WHO report, the most prevalent cancers in men worldwide are colon, stomach, liver, lung, and prostate cancer. In the meantime, stomach, lung, colorectal,

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cervical, and breast cancers have been identified in women. Compared with developed countries, developing countries have a higher cancer death rate. This discrepancy results from variations in risk factors, the efficacy of screening therapies, and treatment accessibility (Street, 2020). Lung cancer is the leading cause of death in males in both developed and developing nations. In contrast, the two diseases that kill women most frequently in both industrialized and developing nations are breast and cervical cancer (Dewi, 2017).

This explanation demonstrates that cancer is the leading cause of mortality among people worldwide. Therefore, alternative therapies are urgently needed to prevent and treat this illness. Numerous investigators have undertaken diverse research endeavors to discover approaches or substitute therapies for cancer prophylaxis and management. Numerous indirect cancer prevention and treatment strategies, including surgery, chemotherapy, radiation, and other techniques, have been developed as a result of the extensive body of research that has already been conducted. However, the side effects of cancer treatment directly affect a patient's physical health, including exhaustion, skin color changes, and severe weight loss (Morita et al., 2016). Numerous studies have been conducted to identify treatments with the fewest possible side effects, because the physical condition of cancer patients is directly affected by the side effects of their treatment.

The conventional procedure can be applied and has few adverse consequences. This is allegedly the result of conventional medicine's efforts to boost the body's resistance, stop cancer from spreading, lessen symptoms, and enhance bodily function. Currently available treatments for cancer include radiation therapy, chemotherapy, and surgery to eradicate diseased cells (Street, 2020). Most individuals are highly interested in traditional medicine as an alternative to treat and prevent cancer because of this notable contrast in their efforts.

As these materials are readily available, most individuals can easily adopt conventional approaches involving natural ingredients for cancer prevention and treatment. In addition to being simple to locate, this procedure has a few adverse consequences. The search for medications that contain natural or herbal substances or anti-cancer chemicals derived from plants is one way to use conventional methods. Herbal plants are supposed to contain therapeutic chemicals that have minimal side effects and are thought to offer an alternative to conventional anticancer treatments. Curcumin is an herbal plant that contains naturally occurring metabolite chemicals with a variety of documented uses, including antiviral, antioxidant, and anticancer properties (Puteri, 2020).

Because curcumin is present in conventional products and spices, it is relatively simple to locate. Turmeric, also known as curcuma domestica val or curcuma longa linn, contains the curcumin chemical, which is a member of the zingiberaceace family. Because they include beta-carotene, polyphenols, flavonoids, and saponins, which are chemicals with anti-cancer properties, turmeric can be utilized as a cancer medication (free radicals). Within the zingiberaceace family, curcuma xanthohiza, popularly referred to as ginger, is another source of curcumin. Ginger rhizomes contain curcumin, which has antioxidant, anti-inflammatory, and anti-tumor properties. This can help to relieve cancer pain. Temulawak extract helps shield the liver from conditions, such as hepatitis B, which can progress to liver cancer (Putri, 2014).

Often present in plants belonging to the genus Curcuma, curcumin, also known as diferuloylmethane, is a polyphenolic molecule with a chemical group (1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione). Curcuminoid extract contains curcumin. The pharmacological benefits of curcuminoid extracts include anti-inflammatory, anti-allergic, anti-dementia, antioxidant, and anti-cancer properties (Abdurrahman, 2019). It is well recognized that curcumin, a component of curcuminoid extract, exhibits anticancer activity on a variety of cancer cell types, including those of the pancreas, ovaries, breast, and colon. This synergistic action of the bioactive components makes the use of curcuminoid extract as an anticancer medication particularly intriguing.

Curcumin's anti-cancer properties are linked to its inhibition of COX and cell signaling pathways, which it does by regulating oxygen and tumor suppressor gene products, and by inducing apoptosis and cell cycle arrest. Additionally, it is linked to its capacity to

impede cell division and its antioxidant, anti-inflammatory, anti-carcinogenesis, immunomodulatory, anti-estrogen, and anti-angiogenesis properties (Mutiah, 2017). Owing to these properties, curcumin is a potent anticancer agent. Additionally, curcumin has been shown by Lin & Lin, (2008) to prevent NF-kB from being induced and to inhibit the growth of multiple myeloma, ovarian, pancreatic, oral, bladder, and prostate cancers, as well as leukemia.

Curcumin is a naturally occurring molecule present in a variety of natural substances or spices and has the potential to be the primary element in traditional medicine for the treatment of cancer. Curcumin, which is present in traditional foods, can be used as an anticancer medication in a variety of ways. Thus, the author of this review article aims to investigate in greater detail the application of curcumin as an anticancer drug for different types of cancer.

RESEARCH METHOD

The method used by the author was a literature review from 5 national and international journals. This method is used with the aim of increasing knowledge and understanding of the topic being discussed by presenting material that has been published by summarizing the material that has been published and providing factual information or new analysis from relevant literature reviews, and then comparing the results in the article. Another method used in this review is the contrast method. The contrast method is a journal/article review method that identifies differences between several research journals and then draws conclusions.

PubMed, ScienceDirect, and Google Scholar are several article sources used to search for information regarding the use of curcumin as an anticancer agent. The majority of articles used were the latest articles written within the last 10 years, namely from 2013-2023. The keywords used in searching these journals are "Curcumin," "Cancer," "Curcumin as an Anticancer," "Utilization of Curcumin as an Anti-Cancer," the initial number of articles found was 15 articles. This resulted in five articles (published from 2012 to 2022) that provided information about cancer and cancer data, curcumin and its uses, as well as the use of curcumin as an anti-cancer agent. Articles were selected based on journals published internationally and indexed by Scopus.

RESULTS AND DISCUSSION

Cancer is associated with aberrant cells that grow out of control. These cells have the ability to metastasize, or spread to other organs, by invading the surrounding cell tissue.Malignant cancer cells have the potential to become fatal. All cell types in the human body can develop into cancer cells. Through connective tissue, blood, nerves, and tissue-supporting organs in the body, cancer cells can spread to other organs. The bodily portion that is impacted faces growth-related challenges (Director General of Disease Control and Environmental Health, 2009).

The treatment options for cancer vary depending on the patient's health status and cancer stage. Surgery, radiation therapy, and chemotherapy are examples of these treatments. The physical health of cancer patients is directly impacted by the treatment they receive; symptoms include extreme weight loss, changes in skin tone, and exhaustion (Morita et al., 2016). Many studies are looking for medicines that can lessen the side effects of cancer treatment, which directly affects the patient's physical condition. These studies have focused on pharmaceuticals that contain anti-cancer chemicals from plants or natural substances.

Curcumin is an herb or natural substance that has been investigated in previous studies and has been shown to have greater metabolite compounds, specificity, and potential for cancer cells. Curcumin, a polyphenolic molecule with a chemical group (1,7-bis (4-hydroxy-3-methoxyphenyl) -1,6-heptadiene-3,5-dione) is frequently found in plants belonging to the curcuma species. This is also referred to as diferuloylmethane. Curcuminoid extract contains curcumin. The pharmacological benefits of the curcuminoid extract include anti-dementia, anti-inflammatory, anti-allergic, antioxidant, and anti-cancer properties. It is

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well recognized that curcumin, a component of curcuminoid extract, exhibits anticancer activity on a variety of cancer cell types, including those of the pancreas, ovaries, breast, and colon. Since the bioactive ingredients can work in concert, there is a lot of promise for using curcuminoid extract as an anticancer medication (Wilken et al., 2011).

Curcumin is a low molecular weight polyphenol that was originally isolated from turmeric in 1815. The structure of differentiuloylmethane was reported in 1910. Curcuminoids, of which curcumin is the primary component, comprise 2–8% of the turmeric content. Several studies have shown that curcumin shields biomembranes against peroxidative damage. Lipid peroxidation is generally caused by a chain reaction mediated by free radicals, which increases cell membrane damage and ultimately alters cellular DNA conditions (Zahra et al., 2020).

Curcumin has been shown to offer therapeutic benefits in a number of chronic conditions, including obesity, metabolic syndrome, liver disease, inflammation, arthritis, neurological illnesses, and most significantly, several forms of cancer. Approximately 12,595 publications (1924–2018) have been published on curcumin; of these, 4,738 (1983–2018) addressed curcumin and cancer, indicating that 37% of the studies have cancer as their main target disease. This information is based on recent bibliographic research. However, the anti-inflammatory and antioxidant properties of curcumin appear to be primarily responsible for the aforementioned actions (Giordano & Tommonaro, 2019).

Researchers and the general public are aware that cancer treatment has advanced over time and now involves more options than chemotherapy or surgery. The primary function of curcumin is to treat cancer without having a negative impact on those who have the disease. Numerous studies have demonstrated the application of curcumin as an inhibitor of cancer cell activity (Abdurrahman, 2019).

The primary goal of this review article is to compile and assess the potential use of curcumin as an anticancer drug. The audience is then informed and educated about the application of curcumin as an anti-cancer agent through this review article. In addition, the purpose of this review was to ascertain the function of curcumin as an anti-cancer agent. Thus, future studies will be easier for other researchers to perform thanks to this study.

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Table I. Journal Review Results

Journal Citation	Research methods	Types of Cancer	Research result
(Ambarsari & Nurcholis, 2019)	The MTT test method (Microtetrazolium Test), which is based on colorimetric principles, was used in this journal article. The capacity of curcuminoid extract and nanoparticles to stop HeLa cell growth was tested cytotoxically using the MTT technique.	**Cervical cancer,** using HeLa cells cultured in RPMI 1640 media added with 10% Fetal Bovine Serum (FBS), 100 U/mL penicillin and 100 µg/mL in 5% CO2, temperature 37°C with air humidity 95% for 2 weeks	It is still unknown how ginger curcuminoid extract inhibits HeLa cells. Research indicates that curcumin, a constituent of ginger curcuminoid extract, is crucial in modulating the activity of the NF-κB and Akt pathways in HeLa cells, thereby inducing apoptosis and suppressing cell growth.Telomerase activity inhibition is another potential mechanism. It is known that HPV-infected cervical cancer cells express the E6 oncogene. The telomerase enzyme is stimulated by the E6 protein (DeFilippis et al., 2003). In human neuroblastoma cells, curcumin has also been shown to decrease telomerase activity. The ability of ginger's curcuminoid extract to stop HeLa cell proliferation has been demonstrated. Curcuminoid extract had the maximum inhibitory action at a concentration of 62.5 ppm, or 93.30%. The cytotoxic effect of curcuminoid extract against HeLa cells can be enhanced by incorporating it into solid lipid nanoparticles. At a concentration of 2 ppm, or 93.43%, nanoparticles have the most activity in inhibiting the development of HeLa cells.
(Jin et al., 2015)	The PI3K/Akt signaling pathway was suppressed and miR-192-5p regulation was increased in this scientific paper to implement this strategy.	**Lung cancer,** by using Human normal NCL-H460 and BEAS-2E lung epithelial cells, and human A549 lung cancer cells were obtained from the Cell Resource Center of the Second Military Medical University.	According to the study's findings, curcumin inhibited the expression of the PI3K/Akt protein in A549 cells, whereas the increase of miR-192-5p expression constrained the expression of the PI3K/Akt protein in A549 cells. In A549 cells, downregulating the expression of miR-192-5p can boost the expression of PI3K/Akt protein. According to this study, curcumin blocks the growth of lung cancer tumors via blocking the PI3K/Akt pathway. This work focuses on curcumin's

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			effects on A549 cells, where it is found to upregulate miR-192-5p and reduce the PI3K signaling pathway/Act, hence preventing cell proliferation and triggering apoptosis of human NSCLC. The findings of this study suggest that curcumin may be a useful therapeutic target for the management of NSCLC. However, because we did not investigate the precise link between miR-192-5p and the PI3K/Akt pathway in lung cancer cells, this study has certain limitations.
(Lianingsih et al., 2020)	The in silico techniques used in this journal paper include molecular docking and virtual screening. The natural compounds curcumin, hesperidin, phiscion, and chrisophanol are used in place of the MAPKs (Mitogen Activated Protein Kinases) pathway subfamily, which includes p38, ERK2, JNK1, and MK-3.	**liver cancer,** using proteins from the subfamily MAPKs (Mitogen activated protein kinases) pathways include p38, ERK2, JNK1 and MK-3 or natural ingredients curcumin, hesperidin, phiscion and chrisophanol.	The findings presented in this article demonstrate the involvement of the MAPKS subfamily targets in liver damage and carcinogenesis. This study explains why pro-inflammatory mediators like LPS are expressed less frequently on HEPG2 when therapeutic candidates like as curcumin, phiscion, chrisopanol, and hesperidin chemicals are present. Studies demonstrate the ability of curcumin, hesperidin, phiscion, and chrisophanol to interact with molecular targets related to inflammation. This chemical has a number of molecular targets that enhance apoptosis in HEPG2 cancer and offer significant promise as a therapeutic treatment for inflammatory diseases. To ascertain whether the chemicals under investigation are efficacious, more in vitro experiments are required.
(Liu et al., 2017)	The MTT test method (Microtetrazolium Test) was used in this journal article. The MTT assay was performed using n tests for invasion, cell cycle, and proliferation in vitro as well as an examination of	**Prostate Cancer,** by using CD44+/CD133+ human prostate cancer stem cells (HuPCaSCs) were isolated from the Du145 and 22RV1 prostate cancer cell lines.	The primary cellular indicator of Curcumin's inhibitory action on HuPCaSCs is the suppression of cell cycle progression. In the meantime, lncRNA-ROR functions as a synergistic regulator of the curcumin target, whereas miR-145 is the direct target of curcumin. Because lncRNA-ROR and Oct4 expression in HuPCaSCs are balanced, normal or high levels of lncRNA-

	xenograft growth in vivo.		ROR expression can attract endogenous miR-145 to sustain high levels of Oct4 expression. This supports the proliferation and invasion of prostate cancer stem cells by maintaining the cell cycle kinase expression and cell cycle progression. Our findings point to a significant epigenetic mechanism by which curcumin inhibits stem cells associated with prostate cancer.
(Taverna et al., 2015)	This was done in this journal paper using both in vitro and in vivo testing. with the use of the MTT, activity, ELISA, motility, and colony formation tests.	**Leukemia Cancer,** using chronic myelogenous leukemia cells, cultured in RPMI 1640 medium.	Findings from scholarly articles Curcumin may have anticancer effects by using exosomes to remove miR-21. This study shown that following Curcumin treatment, CML cells had a drop in miR-21 but not before to miR-21. On the other hand, when curcumin was added, the study detected a rise in miR-21 in exosomes produced by CML cells. The study's findings are consistent with earlier research showing how curcumin affects cancer cell survival by upregulating PTEN and downregulating miR-21. The PI3K-AKT pathway is in opposition to PTEN control, which is brought about by non-genomic processes such as post-transcriptional regulation by non-coding RNAs. The PI-3K-AKT pathway, which regulates proliferation and survival, is impacted by this inhibitory action.

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In 2015, Taverna et al. effects on leukemia cancer found that curcumin is a promising substance that, when paired with traditional tyrosine kinase inhibitors, can enhance the course of treatment in individuals with CML who do not respond to imatinib, the recommended medication for this leukemia. In this study, we demonstrated that treating CML cells with curcumin modulated the miR-21-mediated PTEN/AKT pathway, which in turn inhibited the proliferation of leukemia cells both in vitro and in a natural model. Conversely, curcumin caused BCR-ABL to be downregulated and miR-196b to be upregulated at both the mRNA and protein levels. Researchers have hypothesized that curcumin may function in CML by boosting the clearance of miR-21 from exosomes, which could enhance the antileukemic effect (Taverna et al., 2015).

The inhibitory action of curcumin on HuPCaSCs in prostate cancer is mostly manifested by the prevention of cell cycle progression. In the meantime, lncRNA-ROR functions as a synergistic regulator of the curcumin target, whereas miR-145 is the direct target of curcumin. Because lncRNA-ROR and Oct4 expression in HuPCaSCs are balanced, normal or high levels of lncRNA-ROR expression can attract endogenous miR-145 to sustain high levels of Oct4 expression. This supports the proliferation and invasion of prostate cancer stem cells by maintaining the cell cycle kinase expression and cell cycle progression. However, significant levels of miR-145 can bind directly to Oct4 and reduce its expression when this equilibrium is upset, for example, due to the loss of lncRNA-ROR expression. This inhibited HuPCaSC proliferation and invasion, resulting in cell cycle arrest. Consequently, we identified a key epigenetic mechanism for the biological suppression of prostate cancer progenitor cells by curcumin (Liu et al., 2017).

According to studies on the effect of curcumin on lung cancer, the PI3K/Akt pathway is the mechanism by which curcumin prevents lung cancer tumors from proliferating. MiR-22-3p, miR-143-3p, and miR-192-5p have been found to regulate and participate in the APC, TGFβ, and PI3K pathways in colorectal cancer cells, according to schemadkk. In summary, curcumin inhibits cell proliferation and induces apoptosis in human non-small cell lung cancer (NSCLC) by upregulating miR-192-5p and decreasing the PI3K/Akt signaling pathway in A549 cells. The findings of this study suggest that curcumin may be a useful therapeutic target for the management of NSCLC. However, because the precise link between miR-192-5p and the PI3K/Akt pathway in lung cancer cells was not examined, this study had certain limitations. More research, clinical trials, and extensive statistical analyses are necessary to confirm these findings (Jin et al., 2015).

Molecular docking can provide a rapid and straightforward process for the identification of potential drug candidates from natural substances, such as hesperidin, curcumin, phiscion, and chrysopanol. Virtual screening of natural product drug candidates aids in the discovery of novel molecules and activity of desired compounds (Araújo & Leon, 2001). According to this study, targets of the MAPKS subfamily are involved in carcinogenesis and liver damage. This paper explains how pro-inflammatory mediators such as LPS can be downregulated in HEPG2 or liver cancer by using medications such as curcumin, phiscion, chrisopanol, and hesperidin (Lianingsih et al., 2020).

Curcuminoid extract nanoparticles from ginger coated in solid fat, measuring 648.4 ± 95 nm in particle size and 0.219 in polydispersity index, have been successfully produced through research. These nanoparticles have the potential to fight cancer because they are poisonous, as demonstrated by the Brine Shrimp Lethality Test (BSLT). The objective of this study was to use the MTT assay to assess the anticancer potential of ginger curcuminoid extract nanoparticles against cervical cancer cell lines. The investigation yielded good results, as the proliferation of HeLa cells was inhibited by ginger curcuminoid extract. Curcuminoid extract had the maximum inhibitory action at a concentration of 62.5 ppm, or 93.30%. The cytotoxic action of the curcuminoid extract can be increased by encapsulating it in solid lipid nanoparticles (Ambarsari & Nurcholis, 2019).

CONCLUSION

The literature search results for this article provide evidence that curcumin has potential as an anti-cancer agent. Research journal papers have evaluated curcumin

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molecules in cancer types, such as cervical, prostate, colon, liver, and lung cancer. Given the enormous potential of curcumin as an anticancer agent, expertise and in-depth understanding of the substance are crucial. Researchers are now using the ability of curcumin to suppress cancer cells in various cancer types as a guide to further investigate curcumin chemical. Overall, this study indicates that curcumin primarily functions as an inhibitor of cancer cells, confirming the anti-cancer properties of curcumin.

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