



Moringa oleifera's Effect on Colorectal Cancer

Rolla Al-Shalabi^{1,2}, Nozlana Abdul Samad^{1*}, Lim Vuanghao¹, Ibrahim Al Deeb², Julia Joseph¹

Abstract

Background: *Moringa oleifera*, which is a rich plant with diverse active components, shows promising potential in cancer research, especially concerning colorectal cancer which is a major global cause of mortality. Its phytochemicals, such as flavonoids, phenolic acids, alkaloids, and glucosinolates, contribute to its antioxidant and anti-inflammatory properties, making it a compelling subject of investigation in various fields, including its potential role in combating colorectal cancer. **Methods:** This narrative review was conducted by starting with determining the targeted topics for our research. This was then used as keywords which focused on *Moringa oleifera's* effect on colorectal cancer. The keywords used were: cancer, colorectal cancer, angiogenesis, natural products in cancer and angiogenesis, MO plant, MO as a medicinal plant, MO active component, MO therapeutic potential, and MO effectiveness against colorectal cancer including its leaves, seeds, fruit, and root. After that data was collected from more than 99 articles to identify, summarize, and reflect the target of the research to approve the multiple unique and promising effectiveness of MO against colorectal cancer. **Results:** Research indicates that extracts from different parts of the Moringa plant, such as seeds, leaves, fruits, and roots, exhibit anticancer effects on various colorectal cancer

cell lines through diverse mechanisms. The ability of *Moringa oleifera* as anticancer relies on its phytochemicals, especially antioxidant phenols such as gallic acid, chlorogenic acid, rutin, apigenin, astragaln, quercetin, and kaempferol. **Conclusion:** This review thoroughly explores the impact of different parts of *Moringa oleifera* (leaves, fruits, seeds, roots) on various colorectal cancer cell lines. It confirms the effects of Moringa in regulating cell proliferation, inducing apoptosis, generating reactive oxygen species, and/or modulating the cell cycle. However, the review has not yet definitively confirmed the specific anti-angiogenesis mechanism of Moringa in combatting colorectal cancer. Further research is required to fully elucidate this aspect of its potential in cancer treatment.

Keywords: Antiangiogenesis; Colorectal cancer; Cytotoxicity; Moringa oleifera; Phytochemicals

1. Introduction

Cancer

According to the World Health Organization, Malaysia sees around 48,639 new cases of cancer diagnosed annually, and this number is projected to triple by the year 2040. Globally, cancer stands as one of the leading causes of death. The development of cancer occurs in stages, influenced by various factors (Ganeson et al., 2023; Pongnikorn et al., 2018). Several factors contribute to the body's susceptibility to cancer occurrence. Hormonal changes, cocarcinogen exposure, and tumor promoter effects, such as the conversion of protooncogenes to oncogenes and the inactivation of tumor suppressor genes, play significant roles in cancer development. Additionally, lifestyle behaviors such as smoking, poor nutrition, physical inactivity, and reproductive changes

Significance | The therapeutic benefit of Moringa plant in cancer treatment

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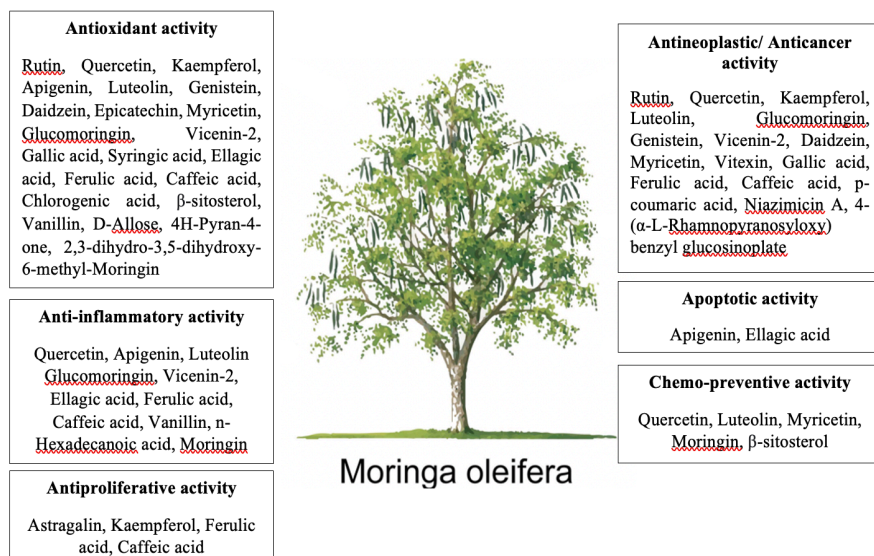


Figure 1. Phytoconstituents responsible for each type of anticancer activity of MO (Singh et al., 2022)

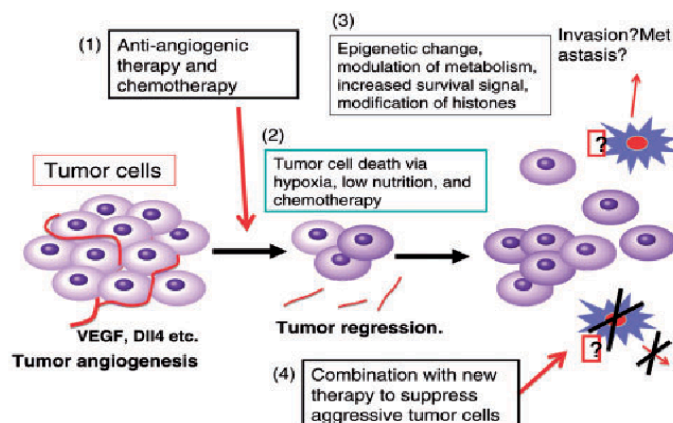


Figure 2. A hypothetical model of tumour responses to anti-angiogenic therapy. The VEGF-VEGFR system plays crucial roles in tumour angiogenesis. Therefore, anti-angiogenic therapy targeting VEGF signals efficiently suppresses cancer progression. However, during therapy, tumour cells may be subjected to hypoxia and/or low nutrient stresses for extended periods, and some of the cells may acquire epigenetic modifications and resistance to these stresses, resulting in a higher cell migration as well as an increased survival signal. (Shibuya, 2013).

Table 1. Pharmacological properties of some phytochemicals present in MO extracts on CRC cells

Phytochemical substance	Molecular mechanism as anticancer	Reference
MO contains morin and chlorogenic acids. Butyric acid was identified as the most abundant metabolite.	antiproliferative	(Caicedo-Lopez et al., 2021)
Flavonoid pigments (kaempferol, rhamnetin, isoquercitrin and kaempferitrin) -glycoside (glucosinolates and isothiocyanates)	Proapoptotic	(Berkovich et al., 2013)
Phenol, eugenol, D-allose, and isopropyl isothiocyanate	antioxidant and anticancer	(Al-Asmari et al., 2015)

further increase the risk of cancer (Katzke et al., 2015; Qin & Xue, 2018). Furthermore, genetic alterations can either be inherited or acquired, and they also contribute to the body's susceptibility to cancer. Combining these genetic factors with unhealthy lifestyle choices can further heighten the risk of cancer occurrence (Aboulthana et al., 2021).

Due to its significant impact on public health, cancer poses a substantial burden. Consequently, there is an immediate and pressing demand to discover and implement effective treatments for this disease (Ganeson et al., 2023).

Colorectal cancer (CRC)

Colorectal cancer (CRC) is the most prevalent type of cancer, with Malaysia reporting 21.32 instances per 100,000 people. Among ethnic groups, Chinese individuals have the highest incidence (27.35), followed by Malays (18.95) and Indians (17.55). Notably, males face a higher risk of developing CRC compared to females, particularly in rectal cancer, where males had a 1.33-times higher age-standardized rate incidence than females (24.16 vs. 18.14 per 100,000, respectively) (Brown & Koh, 2020).

CRC ranks as the second leading cause of cancer-related death in developed countries, accounting for 10% to 15% of all cancers. While significant progress has been made in identifying genetic abnormalities associated with colon cancer's malignant activity, the distribution of colon and rectal cancers is such that 70% occur in the colon and 30% in the rectum (Seol et al., 2014).

Approximately 20% of CRC cases cluster in families and individuals with first-degree relatives diagnosed with colorectal adenomas or invasive CRC. Thus, relatives of individuals diagnosed with CRC have a higher risk of contracting the disease. Lynch syndrome (hereditary nonpolyposis colorectal cancer) and familial adenomatous polyposis are two well-known genetic conditions associated with an increased CRC risk. Thus, it is essential to inquire about family history and risk factors in all colon cancer patients (Vogel et al., 2022).

Inflammation linked to inflammatory bowel disease (IBD) significantly elevates colon cancer risk compared to individuals without IBD. Colon cancer manifests as a malignant growth on the colon's inner wall (Bye et al., 2017; Ni et al., 2013).

Over the last decade, the management of CRC has undergone significant advancements in screening, surgical interventions for reversible disease, and adjuvant chemotherapy (Wils et al., 2001). Consequently, 5-year survival rates have increased from 50% to 62% in the last 25 years (Ozyurt, et al., 2017).

Despite the availability of preventive and therapeutic options, the quest for more precise and effective chemicals which could be extracted or developed from multiple sources such as phytochemical component that extracted from proved effective species such as MO remains crucial to mitigate the adverse effects associated with traditional treatments. Therefore, the development

of innovative compounds and chemicals is essential to reduce mortality rates and enhance treatment outcomes (Islam et al., 2022).

Angiogenesis (hallmarks of cancer)

Krishna and Lopes-Bastos have established a relationship between neo-angiogenesis and cancer growth, laying the framework for a unique anti-tumor strategy (Krishna et al., 2016; Lopes-Bastos et al., 2016). Angiogenesis is a term that refers to the biological process that causes pre-existing blood vessels to grow and formulate new blood vessels. It is a complex network of signaling pathways comprised of enzymes and signaling molecules (Yoo & Kwon, 2013).

For example, during cancer growth, the forming tumor alters the tissue's angiogenic equilibrium, resulting in the secretion of pro-angiogenic chemicals by tumor cells or cells in the tumor microenvironment. Once the tumor reaches a diameter of 1–2 mm and is removed from the blood vessels, the tumor cells undergo apoptosis or necrosis due to a lack of oxygen and nutrition (Kooti et al., 2017). Growth factors and cytokines are the two most prevalent types of mediators that control angiogenesis. Vascular endothelial growth factor (VEGF), tumor necrosis factor-alpha (TNF- α), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), and angiopoietin are a few examples of growth factors. These mediators can be divided into stimulators and inhibitors. The equilibrium between activator and inhibitor mediators is crucial in the angiogenesis pathway (Raju & Kei, 2022; Wang et al., 2019).

Thus, one of the techniques used in cancer treatment is angiogenesis suppression. Angiogenesis inhibitors are one of the most important agents used for reducing tumor growth and metastasis (Raju & Kei, 2022; Wang et al., 2019). They provide a number of advantages over anti-cancer drugs, including fewer side effects, lower resistance, and better accessibility of endothelial cells in blood vessels than tumor cells (El-Kenawi & El-Remessy, 2013).

An example of antiangiogenic agents includes targeted agents like bevacizumab, which is an antibody that acts against the vascular endothelial growth factor. Additionally, cetuximab and panitumumab are antibodies targeting the epidermal growth factor receptor, and they can be utilized in cases of advanced colorectal cancer. These targeted agents show promise in inhibiting angiogenesis and have the potential to improve outcomes for patients with advanced CRC (Kirstein et al., 2014).

Plant extracts are full of bioactive substances that can slow cancer cell development and trigger cancer cell apoptosis by preventing angiogenesis. This may cause cancer to be suppressed or eliminated. Therefore, the development and growth of tumors can be suppressed by phytochemicals. However, research is still needed to investigate and uncover all medicinal plants which possesses antiangiogenic properties (Hoseinkhani et al., 2020).

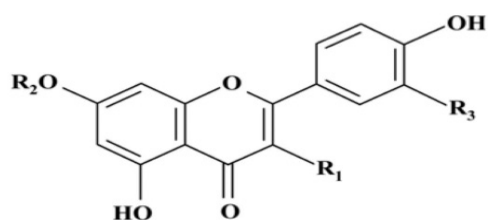


Figure 3. General chemical structure of flavonoids 1 and 2

1: R₁=O-Glc-O-Rha; R₂=H; R₃=OH

2: R₁=OH; R₂=H; R₃=OH

Table 2. Effect of different MO plant parts on many cancer cell lines

Plant part	Cell line	Mechanism of cytotoxicity	Reference
Leaves	HT-29	Inhibition of cell proliferation	Caicedo-Lopez et al., 2021
	HCT116, CACO2, and HCT116P53	ROS generation, Modulation of cell cycle	Reda et al., 2017
	HCT116 and HT-29	Inhibition of cell proliferation	Cuellar-Nuñez et al., 2020
	HCT15, SW48, and SW480	Inhibition of cell proliferation	Tragulpakseerojn et al., 2017
	In-vivo study on CD-1 mice	-	Cuellar-Nuñez et al., 2018
	HCT116	Inhibition of cell proliferation	Tragulpakseerojn et al., 2017
	Caco-2	Inhibition of cell proliferation	Charoensin, 2014
Seeds	T84, HCT-15, SW480 and HT-29	Inhibition of cell proliferation	Mesas et al., 2021
Fruit	HCT116	Induction of apoptosis	Guon & Chung, 2017
Leaf, Seed and Bark	HCT-8	Induction of apoptosis	Al-Asmari et al., 2015
Roots, leaves	HCT 116, Caco-2	Induction of apoptosis	Abd-Rabou et al., 2017

Natural products in cancer and angiogenesis

For oncologists and medical scientists, the challenging task of determining the optimal treatment regimen that effectively targets cancer cells with minimal adverse effects persists. The growing interest in complementary and alternative medicine (CAM) treatment options, with the assumption of lower side effects, has led to the development of a list of phytotherapy medications. Interestingly, about 74% of known anti-cancer medications are derived from various plant species (Rodriguez-Casado et al., 2016). These natural-based anti-cancer medications are valued for their remarkable anticarcinogenic and chemoprotective properties, owing to the presence of specific chemicals that not only exhibit anti-cancer effects but also inhibit the growth of cancer cells, induce cell death, and promote apoptosis. However, despite their potential, only a limited number of natural anti-tumor medicines have undergone thorough examination in clinical trials. Noteworthy plants in this context include camptothecin, vinblastine, vincristine, podophyllotoxin, and paclitaxel (Banerjee et al., 2017; Gezici & Şekeroğlu, 2019).

Among these natural products, *Moringa oleifera* (MO) leaf extracts have gained attention for their antioxidant capabilities (Al-Dabbas et al., 2017).

Overall, the utilization of medicinal plants, including MO, as complementary medicine in cancer care presents a promising avenue for further exploration. These natural compounds have demonstrated potent anticancer properties with reduced toxicity, offering potential benefits to improve cancer treatment outcomes and enhance the quality of life for cancer patients. However, rigorous research and clinical trials are essential to fully understand their mechanisms and ensure their safe and effective integration into cancer therapy protocols (Raju and Kei, 2022).

Moringa oleifera (MO)

MO Leaves is a member of the Moringaceae family, which includes 14 species (*Moringa Arborea* and *M. stenopetala* are native to Kenya; *M. rival*, *M. stenopetala*, and *M. stenopetala* are native to Kenya and Ethiopia; *M. borziana* is native to Somalia and Kenya; *M. pygmaea* is native to Somalia and Kenya (Chukwuebuka et al., 2015; Cohen et al., 2014; Meireles et al., 2020; Zaku et al., 2015).

In the world, *Moringa oleifera* (MO) is one of the most widely studied and farmed plants, having populations in Pakistan, Thailand, Malaysia, Indonesia, North America, West Africa, and Tabuk, Kingdom of Saudi Arabia, among other places (Adebayo et al., 2017a; Al-Asmari et al., 2015).

Numerous names of MO can be found in numerous locations. It is referred to as "The Mother's Best Friend" in Yoruba, "Nuggekai" in Igbo, "Zogale" by Hausa-speaking Nigerians, and "Ewe Ile" in Nigeria, where it is also referred to as "Murungai" in Tamil, "Mashinga Sanga" in Malayalam (Chukwuebuka, 2015).

Furthermore, a "beautiful tree" or "wonder tree," are other common names for MO. It is also known by the name horseradish tree and drumstick (Adebayo et al., 2017).

MO is becoming increasingly popular as a food source. The leaves, fruits, blossoms, and immature pods of this tree, which is known as the "natural nourishment of the tropics," are extremely nutritious and are consumed in many countries, including India, Asia, Pakistan, the Philippines, Hawaii, and many African countries. However, it is a relatively new dietary source in the Western world, having only been introduced in the 1970s (Barakat & Ghazal, 2016; Berkovich et al., 2013).

MO as a medicinal plant

MO leaves are commonly used in traditional medicine for a variety of conditions, including malaria, typhoid fever, parasite infections (including giardia), arthritis (including swellings and sores), skin problems (including acne), genito-urinary disorders (including cystitis), and diabetes (Tiloke et al., 2013).

They're also used to stimulate lactation and to improve the immune system (in order to treat HIV/AIDS symptoms), among other things (Popoola & Obembe, 2013; Nobossé et al., 2018).

However, due to the presence of several phytochemical components in MO, including polyphenols and phenolic acids, flavonoids, glycosides, and possibly alkaloids, as well as a high vitamin, protein, carbohydrate, fatty acid, fiber content, and active components such as astragaloside, isoquercetin, and cryptochlorogenic acid, a growing number of studies have discovered that aqueous, hydro alcohol, or alcohol extracts of MO leaves possess a wide range of additional biological activities including antioxidant, tissue protective (liver, kidneys, heart, testes, and lungs), analgesic, antiulcer, antihypertensive, radioprotective, and immunomodulatory actions (Aboulthana et al., 2021; Cho et al., 2014; Patel et al., 2014; Razis et al., 2014; Stohs & Hartman, 2015; Vongsak et al., 2015).

According to Cuellar-Nuñez et al.; boiled MO dramatically and dose-dependently decreased the incidence and number of tumors (Cuellar-Nuñez et al., 2018). Notably, MO extracts have demonstrated anti-inflammatory, anti-proliferative, and anti-angiogenic properties by reducing IL-6, PCNA, and VEGF-A, respectively (Al Zoubi et al., 2022). This further highlights their potential as a valuable option in cancer treatment. According to a number of investigators, fatty acids and oleic acids in MO has been associated with its chemopreventive activity, which may control cell proliferation and apoptosis in addition to anti-inflammation. All of which are significant in CRC pathogenesis through mechanisms like elevated fatty acid oxidation and interruption of membrane enzymes (Chen et al., 2013).

Moringa's active component

Phytochemical ingredients such as phenolics, flavonoids, tannins, saponins, alkaloids, glycosides, carbohydrates, b-carotene, protein,

vitamin C, calcium, potassium, and triterpenoids, particularly those found in the human diet, have been shown to have antimutagenic and anticarcinogenic properties.

Karthivashan et al. (2013) conducted an analysis using HPLC-DAD-ESI_MS/MS, which confirmed the presence of multiflorin-B, apigenin-8-C-glucoside, quercetin, and kampferol derivatives in the crude hydro-ethanolic extract of MO leaves (Karthivashan et al., 2013). Likewise, an HPLC analysis identified seven polyphenols, namely gallic acid, chlorogenic acid, luteolin, rutin, quercetin, kampferol, and apigenin, in the methanolic extract of MO (Valdez-Solana et al., 2015). Additionally, quinic acid, quercetin, and kampferol were discovered in both the reproductive and vegetative tissues of MO, including the leaves and stem (Maldini et al., 2014).

Figure 1 presents a compilation of the primary phytochemicals found in MO that are responsible for its various biological effects (Biswas et al., 2020; Vongsak et al., 2013).

The therapeutic potential of *Moringa oleifera* plays a crucial role in its anticancer activity

Antioxidant Properties

MO leaves are very nutrient-dense as they are a rich source of natural antioxidants such as β -carotene, Vitamin C, protein, iron, and potassium. They work either directly by minimizing the tissue's oxidative stress through scavenging the free radicals, or indirectly by strengthening the natural cellular defenses. According to epidemiological studies; the consumption of natural antioxidant sources like MO is associated with a lower risk of cancers, cardiovascular diseases, neurological illnesses, aging, asthma and inflammation (Peñalver et al., 2022). In a study conducted by Peñalver et al.; the antioxidant activity of MO leaves was examined by using a number of well-established in vitro systems, such as β -Carotene bleaching, reducing power, DPPH/superoxide/hydroxyl radical scavenging, ferrous ion chelation and lipid peroxidation (Peñalver et al., 2022). MO leaf extract (MOEF) caused a reduction in the levels of lipid peroxides (LPO) and an elevation in the levels of glutathione (GSH), therefore, the leaf extract demonstrated concentration-dependent antioxidant activity against oxidative DNA damage. In addition, MOEF was able to mitigate the toxicity caused by CCl₄ injection.

According to the HPLC analysis, the leaf extract was rich with flavonoids (kaempferol, quercetin and rutin) and phenolic acids (gallic, chlorogenic, ellagic, and ferulic acid). Hence, it can be said that the MOEF have significant phenolic content and strong antioxidant capabilities, which may be mediated by both metal chelation and direct scavenging of free radicals (Peñalver et al., 2022).

The successive aqueous extract of MO exhibited strong scavenging effect on 2, 2-diphenyl-2-picryl hydrazyl (DPPH) free radical, superoxide, nitric oxide radical and inhibition of lipid

peroxidation. Results suggests that the extracts of MO both mature and tender leaves have potent antioxidant activity against free radicals, prevent oxidative damage to major biomolecules and afford significant protection against oxidative damage (Nobossé et al., 2018).

Anti-inflammatory Properties

It is possible that a number of bioactive chemicals contained in MO leaves, such as flavonoids and phenolic acids, may potentially contribute to the anti-inflammatory process (Leone et al., 2015; Luetragoon et al., 2020).

MO leaf extracts (concentrate, ethyl acetate, and isothiocyanates) have been shown to suppress human macrophage cytokine production, reduce expression of inducible nitric oxide synthase, reduce gene expression, and inflammatory marker production (TNF- α , IL-6, IL-1, and IL-8) in the same way that aspirin does (Coppin et al., 2013; Kooltheat et al., 2014; Kumar Gupta et al., 2013; Waterman et al., 2015).

Cytotoxic Properties

MO leaf extract is one of the anti-tumor medications currently being tested in clinical trials, which increases the efficacy of chemotherapy in human cancer cells. As mentioned earlier in this review, it is known that MO contains several different chemicals, with some of them being particularly beneficial because of their therapeutic properties. The antioxidant phenols are mostly responsible for its potential to cause apoptosis in cancer cells. These substances function by inducing the activity of anti-apoptotic proteins like Bcl2, IAPs (an apoptosis inhibitor), FLIP, and caspases as well as pro-apoptotic proteins like TRAIL, bax, and bad (Adebayo et al., 2017).

Kaempferol, rhamnetin, isoquercitrin, and kaempferitrin are some of the flavonoid pigments found in the leaves of MO. They have the ability to protect organisms and cells against oxidative DNA damage, which has been linked to cancer and degenerative diseases in a number of studies (Sikder et al., 2013). Furthermore, these leaves include a significant concentration of glycoside chemicals, glucosinolates, and isothiocyanates, as well as glycerol-1-(9-octadecanoate), 3-O-(6'-O-oleoyl-beta-D-glucopyranosyl), and beta-sitosterol, among other compounds. Therefore, it has been demonstrated that MO leaf extract has a significant anti-tumor effect (Berkovich et al., 2013).

Studies exploring the anticancer effects of MO extracts in various models, including breast cancer, leukemia, hepatocarcinoma, and colorectal malignancies, have revealed no toxicity signals in normal cells despite its activity against cancer cells which indicated its selective cytotoxic effect, and therefore, its safety for healthy cells (Al-Asmari et al., 2015; Biswas et al., Elsayed et al., 2016; 2020; Jafarain et al., 2014; Jung et al., 2014).

Antiangiogenic Properties of Moringa

Researchers have thoroughly investigated and documented the anti-cancer properties of MO leaves, but the antiangiogenic properties have received far less attention (Krishnamurthy et al., 2015; Welch et al., 2017). By reducing IL-6, PCNA, and VEGF-A, respectively, MO extracts had anti-inflammatory, anti-proliferative, and anti-angiogenesis impacts on cancer tissues (Al Zoubi et al., 2022).

Raju & Kei studied the antiangiogenic activity of different MO extracts; 50% and 100% methanol extract, 50% and 100% aqueous extract, in addition to a positive control group (sunitinib). The 100% aqueous extract of MO had the greatest anti-angiogenic activity of all the extracts, leading to a larger percentage reduction in blood vessels (81.33%) after 48 hours of therapy. Furthermore, it was discovered that increasing the concentration of the MO extract improved the anti-angiogenic impact of MO leaves. Several phytochemicals contained in MO leaves were discovered to have anti-angiogenic activity (Raju & Kei, 2022).

Further studies showed that essential oils from MO and *M. peregrina* seeds have anti-angiogenic activity, which can help prevent the growth of cancer (Elsayed et al., 2020).

Moreover, to evaluate the anti-angiogenesis action, Dharani et al. evaluated the ethanolic extract of MO on CAM surface at 5 µg and 10 µg. The extract demonstrated considerable antiangiogenic action at the studied doses, earning scores of 0.5 for 5 µg and 2.0 for 10 µg extract. The findings of this study demonstrate unequivocally that ethanolic leaf extract from MO demonstrated a strong antiangiogenic action (Dharani et al., 2014).

Moringa effects on Colorectal cancer

As previously stated, research indicates that MO might possess promising anticancer properties, particularly concerning colorectal cancer. The plant's active constituents have demonstrated the ability to impede cancer cell proliferation, trigger apoptosis, and hinder tumor formation. Nevertheless, it is crucial to emphasize that investigations in this domain are still at a preliminary phase, and further extensive studies are imperative to gain a comprehensive understanding of the mechanisms and potential advantages involved (Khor et al., 2018).

The process by which phytochemical extracts from *Moringa oleifera* leaves exert cytotoxicity against colorectal cancer cells is likely intricate and may involve multiple pathways. However, several potential mechanisms have been suggested to contribute to their cytotoxic effects:

Firstly, the induction of apoptosis: The phytochemicals present in the extracts have the potential to trigger apoptosis, which is a programmed cell death, in colorectal cancer cells. This can result in the controlled elimination of cancer cells. The effectiveness of *Moringa oleifera* in inducing apoptosis is largely influenced by the

antioxidant capacities of its phytochemical constituents, primarily natural phenolic compounds (Lu et al., 2013).

Another mechanism involves the modulation of the cell cycle: The extracts from *Moringa oleifera* may disrupt the normal progression of the cell cycle in cancer cells, causing them to be arrested at specific phases and preventing their uncontrolled growth. In a study by Reda et al., the effect of MO leaf extract on three colon cancer cell lines (HCT116, CACO2, and HCT116P53) was investigated in terms of tumor suppression. It was observed that MO led to a modulation of the cell cycle in these cancer cells, resulting in inhibition at the sub-G0 phase and eventually leading to cell death (Reda et al., 2017).

Additionally, the extracts might inhibit cell proliferation: By interfering with the signaling pathways that regulate cell division and growth, the extracts can reduce cancer cell proliferation. Tragulpakseerojn et al. (2017) discovered that the leaf extract of *Moringa oleifera* exhibited potent anti-proliferative activity on the human colon carcinoma HCT116 cell line, and its mechanism of action involved a reduction in ERK1/2 phosphorylation (Tragulpakseerojn et al., 2017).

Moreover, the plant can exhibit Anti-angiogenic effects: Certain phytochemicals have demonstrated the ability to hinder the formation of new blood vessels (angiogenesis) that provide nutrients to tumors. By cutting off the tumor's blood supply, the extracts can impede its growth and survival. Raju & Kei conducted a study on the antiangiogenic activity of various MO extracts. Among them, the aqueous extract exhibited the most potent anti-angiogenic activity, leading to a significant reduction in blood vessels in a concentration-dependent manner. This effect can be attributed to several phytochemicals present in MO leaves that were found to possess anti-angiogenic properties (Raju & Kei, 2022).

Another mechanism involves ROS generation: The extracts can induce the production of reactive oxygen species (ROS) in cancer cells, leading to oxidative stress. Excessive oxidative stress can cause damage to cellular components and trigger cell death. In the research conducted by Reda et al., the impact of MO leaf extract on three colon cancer cell lines (HCT116, CACO2, and HCT116P53) was investigated in terms of tumor suppression. The MO extract was found to increase oxidative stress by promoting ROS generation, and, in combination with the disruption of membrane integrity caused by the extracts, this contributed to the demise of cancer cells (Reda et al., 2017).

Additional mechanisms could involve the regulation of the immune system: Phytochemicals have the potential to activate the immune system, enhancing its ability to recognize and eliminate cancer cells.

Moreover, the extracts may inhibit specific signaling pathways: Certain phytochemicals can specifically target key signaling pathways essential for the survival and growth of cancer cells.

In conclusion, the study revealed that the diverse phytochemicals present in the extracts may operate through different mechanisms, and their collective actions could contribute to the overall cytotoxicity against colorectal cancer cells (Colic & Pavelic, 2000). Table 1 depicted the molecular mechanisms of cytotoxicity exhibited by certain phytochemicals found in *Moringa oleifera* extracts.

Moringa Leaves on CRC

MO leaf extracts have exhibited anticancer properties against CRC cells as well. These extracts have demonstrated the ability to suppress cell proliferation and induce apoptosis in laboratory studies. Additionally, MO was observed to downregulate proinflammatory mediators that offer protection against colon carcinogenesis (Cuellar-Núñez et al., 2021).

According to Al-Asmari et al., Moringa leaf and bark extracts have anti-cancer effects against the HCT-8 cell line, which can be exploited to create novel medications for the management of CRC. The apoptosis assays revealed a notable rise in the proportion of apoptotic cells in HCT-8 cell line (Al-Asmari et al., 2015). Furthermore, the MO leaves extract exhibited potent anti-cancer activity against the HT-29 cell line (Caicedo-Lopez et al., 2021).

Moringa leaves reduced the activity of damaging fecal enzymes (β -glucosidase, β -glucuronidase, tryptophanase and urease) besides reducing the prevalence of tumors in male CD1-mice (~ 50% with 5% w/v of moringa dose). These results imply that phenolic compounds and total dietary fiber, two bioactive components of moringa, might have chemopreventive properties (Cuellar-Núñez et al., 2018).

Reda et al. investigated how MO leaves extract affected three colon cancer cell lines in terms of tumor suppression (HCT116, CACO2, and HCT116P53). At sub G0 phase, all three cell lines were inhibited. The increased oxidative stress, loss of membrane integrity, and subG0 phase cell cycle arrest caused by the extract resulted in cell death (Reda et al., 2017).

Tragulpakseerojn et al. (2017) investigated the in vitro antiproliferative effect of MO methanolic leaf extract on the human colon carcinoma HCT116 cell line and explore its mechanism of action.

The results indicated that the MO leaf extract displayed robust anti-proliferative activity, and its mechanism of action involved reducing ERK1/2 phosphorylation (Tragulpakseerojn et al., 2017).

Tragulpakseerojn et al. (2017) investigated the inhibitory effect of aqueous and ethanol extracts from MO leaves on the proliferation of colon cancer cells. The antiproliferative effect of the extracts was tested on three types of colon cancer cell lines: HCT15, SW48, and SW480. The extracts were tested at concentrations of 100, 250,

500, and 1,000 μ g/ml for 24, 48, and 72 hours using MTT assay. The results revealed that both extracts exhibited toxicity towards all tested cell lines, with the inhibitory effect increasing with higher concentrations and longer exposure times. Furthermore, the ethanol extract of MO demonstrated better antiproliferative results on all tested cell lines compared to the aqueous extract. Among the cell lines, SW48 was found to be the most sensitive to the extracts' effects (Tragulpakseerojn et al., 2017).

Cuellar-Núñez et al. (2020) aimed to comparatively assess the antiproliferative effects of different MO leaf extracts on HCT116 and HT-29 human colorectal cancer cells. The calculated IC50 values ranged from 0.17 to 3.17 mg/mL, indicating that MO leaf extracts displayed significant antiproliferative effects on colon cancer cells. These findings demonstrate the potential of MO leaf extracts, especially the glucosinolate-rich hydrolyzed extract, as promising candidates for combating colon cancer by inducing apoptosis and reducing pro-inflammatory cytokines (Cuellar-Núñez et al., 2020).

Althomali synthesized MO-AgNPs and compared them with MO leaf extract for their effects on a cancerous cell line. The results revealed that the MO-AgNPs led to a decrease in the expression of CTNNA1 and LRP6 genes in both cell lines. Interestingly, the expression of the LRP5 gene increased in response to both treatments. Furthermore, the treatment had divergent effects on the APC gene expression in the two cell lines. In SW480 cells, the APC gene expression decreased after treatment, while in HCT116 cells, it increased (Althomali et al., 2022).

Charoensin conducted a two-stage successive extraction of phytochemicals from MO leaves using methanol and dichloromethane solvents. The obtained extracts were then evaluated for their ability to inhibit the growth of colorectal cancer cells (Caco-2). The results revealed that both extracts effectively and significantly inhibited the proliferation of cancer cells in a dose-dependent manner. Additionally, when tested on normal human dermal fibroblast cells, the extracts had no adverse effect on cell growth, indicating their selective anti-cancer properties (Charoensin, 2014).

Moringa Seeds on CRC

MO seed extracts have shown encouraging antiproliferative effects on different colorectal cancer cell lines such as HT-29, HCT-116, SW480, DLD-1, Caco-2, RKO, LS174T, COLO205, SW620, and LoVo. These extracts have been observed to hinder cell growth and prompt cell death in a manner that depends on the dosage applied.

Using the CRC cell lines T84, HCT-15, SW480, and HT-29, Mesas et al. investigated the anticancer effects of ethanolic extracts of the seeds of MO. Of the examined cancer cell lines, MO extracts had the most antioxidant and antiproliferative effects (Mesas et al., 2021).

In a study by Charoensin et al. (2014), the researchers aimed to investigate the potential activity of methanolic and ethanolic extracts from MO. They specifically focused on the phenolics content and antioxidant activity in different parts of the MO, including the seeds, skin, pulp, and seed coat.

The results provide valuable insights into the activity of MO extracts, particularly focusing on the seed coat of MO, which showed the most potent growth inhibition and tetrazolium salt reduction. The inhibition of growth was more pronounced at low concentrations of the extract, but at high concentrations, the effect appeared to be reversed (Charoensin et al., 2014).

Moringa Fruit on CRC

Guon and Chung conducted a study on the cytotoxic effect of MO fruits and their flavonoids 1 and 2 (Figure 3). The researchers found that the ethanolic extracts from the fruits reduced the viability of HCT116 human colon cancer cells by 38.5% at a concentration of 150 µg/mL, and this reduction was observed in a concentration-dependent manner. Additionally, the treated cells exhibited apoptotic features, such as cell shrinkage and decreased cell size. Based on these findings, the researchers suggest that the 70% ethanolic extracts of MO fruits, along with flavonoids 1 and 2, show promise as potential cytotoxic agents in the context of CRC therapy (Guon & Chung, 2017).

Moringa Roots on CRC

While not as extensively studied as other components of the plant, extracts from MO roots have shown promise in exerting anti-cancer effects on CRC cells. However, additional research is necessary to fully comprehend the specific mechanisms underlying these effects.

Abd-Rabou et al. (2017) aimed to assess the activity of various extracts obtained from MO leaves, its PEG nanocomposites (MLn), as well as the root core (Rc) and outer (Ro) parts against colorectal HCT 116/Caco-2 cells in laboratory settings. The researchers investigated the cytotoxic effects of these extracts by examining their impact on apoptosis. The results revealed that all extracts displayed distinct ratios of cancer cell death. Surprisingly, the root core extract exhibited the highest efficacy, killing a significant proportion of cancer cells (approximately 70-80%), while having minimal inhibitory effects on normal BHK-21 cells (approximately 30-40%). The observed increase in apoptotic cells further confirmed the cytotoxic effects of these extracts on HCT 116 cells (Rc: 212% and Ro: 180%, respectively) when compared to the control group (100%) (Abd-Rabou et al., 2017).

Table 2 provides a summary of the anticancer effects of various parts of *Moringa oleifera* on different colorectal cancer cell lines.

Conclusion

This study reveals the anticancer potential of various parts of MO against CRC cell lines. The MO extract contains a range of

phytochemicals, including alkaloids, saponins, steroids, flavonoids, and tannins, which are believed to be responsible for its anticancer effects. Numerous studies have demonstrated significant cytotoxicity toward cancer cells treated with MO extracts. The results of this research indicate that the MO extract holds promising anti-cancer properties, suggesting its potential application in the management of CRC, as per guidelines.

Author Contributions

Rolla Al-Shalabi wrote the manuscript, Nozlena Abdul Samad reviewed, edited the manuscript, and supervised the study, Lim Vuanghao and Ibrahim Al-Deeb reviewed and supervised the study, Julia Joseph reviewed and edited the manuscript.

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Competing financial interests

The authors have no conflict of interest.

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