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Review

Therapeutic Strategies for Colorectal Cancer in Saudi Arabia: The Role of Natural and Synthetic Compounds

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Abstract: Colorectal cancer (CRC) is a major public health concern in Saudi Arabia, with rising incidence rates and limited treatment responsiveness in advanced stages. This review presents an in-depth analysis of preclinical and experimental research conducted within the region, focusing on natural products and synthetic compounds with therapeutic potential. Plant-derived extracts, marine bioactives, and engineered molecules have shown efficacy in inducing apoptosis, arresting the cell cycle, and modulating critical signaling pathways in CRC models. Additionally, novel nanotechnology-based delivery systems and combination therapies are emerging as promising approaches to overcome drug resistance and improve treatment precision. This review highlights translational research directions and underscores the need for clinical validation of these compounds to enhance CRC management and patient outcomes in Saudi Arabia.

Keywords: colorectal cancer; Saudi Arabia; natural products; synthetic compounds; therapeutic strategies; nanotechnology; chemoresistance

1. Study Aims

This review aims to deliver an in-depth and critically evaluated synthesis of colorectal cancer (CRC) research in Saudi Arabia, highlighting the emerging therapeutic promise of both natural bioactives and synthetic compounds. By examining recent preclinical advancements, this study identifies novel molecular targets, innovative drug candidates, and multimodal treatment approaches tailored to regional disease patterns. Emphasis is placed on the translational relevance of these findings, including their potential to overcome chemoresistance, enhance efficacy, and improve patient-centered outcomes. Furthermore, this analysis underscores the need for clinical trials to validate safety and therapeutic impact, paving the way for integrative, evidence-based CRC management strategies in the region.

2. Introduction

Colorectal cancer (CRC) is a significant global health concern, ranking among the leading causes of cancer-related mortality [1]. Recent worldwide cancer data indicate roughly 1.9 million new cases of CRC each year, highlighting its enormous contribution to global health burdens [2]. In Saudi Arabia, CRC is notably predominant among male populations and ranks third among women, with increasing rates observed in younger demographics [2]. These alarming trends highlight the need for

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enhanced prevention and innovative therapeutic approaches tailored to regional epidemiological profiles.

The pathogenesis of CRC involves a complex interplay of genetic predispositions, environmental exposures, and lifestyle behaviours such as excess weight, tobacco use, and physical inactivity [3]. Despite advancements in conventional treatments like chemotherapy and targeted therapies, challenges persist, including drug resistance, toxicity, and high recurrence rates [4,5]. These limitations have prompted exploration into alternative therapeutic strategies, notably Immunotherapies such as Immune checkpoint inhibitors, chimeric antigen receptor (CAR)-T cell therapies, and CRC-specific vaccines, which aim to enhance treatment efficacy and overcome resistance mechanisms [6].

Natural products derived from plants, marine life, and microorganisms have emerged as promising candidates in CRC treatment due to their diverse bioactive properties, including anti-inflammatory, cytotoxic, and apoptosis-inducing activities [7]. Key bioactive compounds like Alkaloids, flavonoids, and terpenes have demonstrated notable anti-cancer effects across various biological [8,9]. In parallel, the development of synthetic compounds, including small-molecule inhibitors and targeted therapies, has opened new avenues for CRC management [10]. The strategic combination of natural and synthetic compounds presents a multi-targeted approach to enhance therapeutic efficacy and reduce resistance.

Research efforts in Saudi Arabia have increasingly focused on evaluating plant-based extracts, marine bioactives, and synthetic molecules for their anti-CRC potential. Notable examples include Nigella sativa, Moringa oleifera, and various marine-derived metabolites, which have demonstrated anti-cancer activities, through apoptosis, cell cycle arrest, and suppression of key signalling pathways. Specifically, Nigella sativa has been observed to inhibit NF-κB and AP-1 pathways, while extracts from Moringa oleifera are known to trigger G2/M phase arrest and promote programmed cell death. Additionally, bioactive substances isolated from marine environments have been linked to overcoming Multidrug resistance in cancer cells [7,11]. Recent studies have also highlighted the marine bacterium Halomonas meridiana as an exceptional producer of L-glutaminase, an enzyme capable of depriving colorectal adenocarcinoma cells of L-glutamine, a critical nutrient for tumour growth. Experimental findings revealed that L-glutaminase significantly reduced cell viability in CRC lines such as (LS 174 T and HCT 116), inducing apoptosis at multiple stages. These discoveries underscore the therapeutic potential of marine-derived bioactives in CRC management, suggesting a valuable expansion of natural product-based interventions [12].

Beyond natural compounds, synthetic drugs have been strategically designed to interfere with specific biochemical pathways involved in colorectal cancer progression. Among them, compounds 4 and 16 have demonstrated notable cytotoxic effects against colorectal cancer (HCT116) cell lines, positioning them as promising candidates for the development of new therapeutic agents [13]. Furthermore, Synthetic benzoxazole derivatives have exhibited both antimicrobial and anticancer properties, reinforcing their potential utility in CRC treatment.

Nanotechnology has revolutionized modern medicine by significantly enhancing drug delivery mechanisms and boosting the therapeutic efficacy of anticancer agents. In colorectal cancer therapy, nanoparticles are employed to improve site-specific drug targeting, enhance multimodal treatment strategies, and effectively combat drug resistance and metastatic progression [14]. Despite its therapeutic potential, nanotechnology presents challenges, including concerns about toxicity, long-term safety, and the complexity of large-scale manufacturing. Nevertheless, the integration of nanotechnology-based drug delivery systems in colorectal cancer management has the potential to optimize the clinical utility of both natural and synthetic therapeutics, reducing systemic toxicity while maximizing therapeutic precision [15].

This review aims to deliver an in-depth and critically evaluated synthesis of colorectal cancer (CRC) research in Saudi Arabia, highlighting the emerging therapeutic promise of both natural bioactives and synthetic compounds. This study identifies novel molecular targets, innovative drug candidates, and multimodal treatment approaches tailored to regional disease patterns by examining

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recent preclinical advancements. Emphasis is placed on the translational relevance of these findings, including their potential to overcome chemoresistance, enhance efficacy, and improve patient-centered outcomes. Furthermore, this analysis underscores the need for clinical trials to validate safety and therapeutic impact, paving the way for integrative, evidence-based CRC management strategies in the region.

3. Natural Products and Their Application

Natural products have emerged as potent therapeutic candidates in colorectal cancer (CRC) treatment due to their broad spectrum of bioactive compounds with anti-inflammatory properties. In Saudi Arabia, several studies have focused on plant-derived extracts and marine bioactives to explore their anti-CRC capabilities. This section discusses key findings from in vitro and in vivo studies conducted in the region.

3.1. In Vitro Studies

Nigella sativa (black seed) and crude saponin extract (CSENS):

Nigella sativa, commonly known as black seed, has demonstrated significant anti-cancer effects against HCT116 colorectal cancer cells. Crude saponin extract (CSENS) derived from this plant exhibited anti-proliferative and apoptotic properties, primarily through the modulation of key signaling pathways, including NF-κB, AP-1, Nrf2, and Bax/Bcl-2 regulation [7]. These findings suggest that Nigella sativa may serve as an effective adjunct therapy for CRC.

Olive leaf extract (Olea europaea):

Olive leaf extract, rich in chlorogenic acid, has been shown to inhibit the growth and migration of HT29 colorectal cancer cells. Experimental data indicate that the extract induces DNA fragmentation, causes S-phase cell cycle arrest, and elevates reactive oxygen species (ROS) production, supporting its potential as an anti-cancer agent [16].

Ferula hermonis root extract (FHRH):

The root hexane extract of Ferula hermonis demonstrated dose-dependent cytotoxicity against (LoVo) colon cancer cells. Mechanistic studies revealed that FHRH triggers apoptosis through caspase 3/7 activation and modulates gene expression involved in cell death pathways [17].

Flavonoids in colorectal cancer treatment:

Flavonoids, a diverse group of polyphenolic compounds, are well-regarded for their anti-cancer potential due to their ability to promote apoptosis, inhibit proliferation, and modulate cellular pathways. Their high bioavailability and low toxicity profiles render them promising candidates for CRC therapy, encouraging further exploration into their therapeutic applications [8].

Green synthesized silver nanoparticles (AgNPs):

The application of green synthesis for the development of silver nanoparticles (AgNPs) using *Lasiurus scindicus* and *panicum turgidum* seed extracts has been explored for its anticancer potential. Characterized through DLS and TEM techniques, these biosynthesized nanotechnology with phytochemicals marks a promising strategy for enhancing CRC treatment through improved delivery and reduced toxicity [18].

Selaginella repanda Ethanolic Extract:

Ethanolic crude extract of *Selaginella repanda* has demonstrated potent anticancer effects against HCT116 cells in a manner that is both dose- and time-dependent. Phytochemical analysis identified the presence of key bioactive compounds, including flavonoids, alkaloids, terpenoids, and phenolics, contributing to its observed efficacy. Its favorable pharmacokinetics profile and low toxicity suggest potential for further development as a CRC therapeutic [19].

Sansevieria trifasciata Extract:

The ethanolic extract of *Sansevieria trifasciata* leaves has been observed to selectively target HCT116 colorectal cancer cells, demonstrating higher cytotoxicity compared to normal colon

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epithelial cells. The significantly low IC50 values indicate its potential as a safe and effective candidate for CRC treatment [20].

Tetraclinis articulata Essential Oil:

Essential oil extracted from the trunk bark of *Tetraclinis articulata* displayed its moderate cytotoxic activity against SW620 colorectal carcinoma cells. The fractions with IC50 values below 30 µg/mL were particularly active, primarily due to the presence of oxygenated sesquiterpenes, such as caryophyllene oxide and carotol [21].

Moringa oleifera Leaf and Bark Extracts:

Extracts from leaf and bark of Moringa oleifera, collected from Saudi Arabia, have demonstrated promising anticancer activity against HCT-8 colorectal cancer cells. Experimental findings revealed a reduction in cell viability, induction of apoptosis, and G2/M phase cell cycle arrest. Phytochemical analysis using GC-MS identified eugenol and D-allose as the primary active components contributing to its anti-cancer properties [11].

Ziziphus nummularia Ethanolic Extract:

The ethanolic extract *of Ziziphus nummularia* was found to exert strong anti-cancer activity against HCT8 cells through mechanisms involving apoptosis and microtubule distribution. Luteolin-7-O-glucoside, identified as a key active compound, was shown to inhibit tubulin polymerization, causing M-phase arrest. positioning this plant as a potential source for novel anticancer agents [22].

Rhazya stricta Alkaloid Extract (CAERS):

Alkaloid extract from *Rhazya stricta* demonstrated significant inhibition of cell proliferation and induced apoptosis in HCT116 colorectal cancer cells. Mechanistic analysis indicated that CAERS downregulated NF-κB, AP-1, ERK MAPK pathways while enhancing the expression of pro-apoptotic markers p53, p21, Bax, and caspases, supporting its role as a promising chemotherapeutic agent [23].

In addition to specific plant extracts, alkaloids, a key class of phytoconstituents, have been intensively studied for their ability to promote ROS-mediated apoptosis in colon cancer cells. These chemicals increase intracellular ROS levels, alter redox equilibrium, and initiate apoptotic pathways that target factors like IGF-1, making them a viable therapeutic strategy with low toxicity to normal cells [24].

Table 1. In vitro studies of natural products against colorectal cancer cell lines, highlighting mechanisms of action and target pathways.

Natural product	Study type	Target cell line(s)	Key mechanism/findings	Author
Nigella sativa (CSENS extract)	In vitro	HCT116	Induced apoptosis via NF-κB, AP-1, Nrf2 modulation; Bax/Bcl-2 regulation	Ayman I Elkady,2015
Olive Leaf Extract (chlorogenic acid)	In vitro	HT29	Induced S-phase arrest, ROS generation, apoptosis	Albogami, S., 2021
Ferula hermonis (FHRH extract)	In vitro	LoVo	Caspase 3/7 activation; apoptosis; bioactive compounds identified (Alpha-Bisabolol, Baccatin III)	Abutaha, N., Nasr;2019
Flavonoids (general)	In vitro	Various colon cancer lines	Promoted apoptosis, suppressed proliferation via multiple pathways	Mariam Abotaleb,2018

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AgNPs (*Lasiurus scindicus* and *Panicum turgidum*)	In vitro	HCT116	Green-synthesized nanoparticles showed cytotoxicity against cancer cells	Alburae, N., 2024
Selaginella repanda (ethanolic extract)	In vitro	HCT116	Induced apoptosis, dose/time dependent cytotoxicity, favorable pharmacokinetics	Adnan, M., 2021
Sansevieria trifasciata (ethanolic extract)	IN VITRO	HCT116	Selective cytotoxicity toward cancer cells, reduced IC50 vs. normal colon cells	Afzal, S., 2024
Tetraclinis articulata (essential oil)	In vitro	SW620	Moderate cytotoxicity (IC50 < 30 µg/mL), attributed to oxygenated sesquiterpenes (caryophyllene oxide, carotol)	Jlizi S, 2021
Moringa oleifera (leaf and bark extracts)	In vitro	HCT-8	Induced apoptosis, G2/M phase arrest, bioactive compounds (eugenol, D-allose)	Abdulrahman Khazim Al-Asmari,2015
Ziziphus nummularia (ethanolic extract)	In vitro	HCT8	Apoptosis induction; microtubule disruption via luteolin-7-O-glucoside	Alghamdi, S.S., 2024
Rhazya stricta (CAERS extract)	In vitro	HCT116	Downregulated NF-κB/AP-1; upregulated p53, caspase-3/7/9, Bax	Elkady, A.I., 2016

3.2. In Vivo Studies

While extensive in vitro studies have demonstrated the potential of natural products against colorectal cancer (CRC), fewer in vivo studies have been conducted, particularly within Saudi Arabia. The following subsections detail the promising findings from animal models, emphasizing the anti-tumor capabilities of various natural extracts.

Ferula hermonis Root Extract (FHRH):

Preclinical investigations have explored the anti-cancer properties of *Ferula hermonis* root extract in rodent models. In a DMBA-induced mammary tumor model, FHRH exhibited notable tumor-suppressing activity, providing preliminary evidence for its potential use in CRC models. These findings encourage further exploration of Ferula hermonis in more CRC-specific in vivo settings to validate its therapeutic efficacy and safety [17].

Ferula assa-foetida OGR Extract:

The oleo-gum-resin (OGR) extract of *Ferula assa-foetida* has been evaluated for its anti-tumor properties in a xenograft mouse model using HT-29 colorectal cancer cells. Treatment with this extract resulted in a marked reduction in tumor volume, underscoring its potential as a therapeutic agent for CRC [25]. This promising data supports further translational research to validate its mechanism of action and clinical relevance.

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Arthrocnemum machrostachyum Methanolic Extract (AME):

Methanolic extract of *Arthrocnemum machrostachyum* demonstrated strong anti-tumor activity in an Ehrlich solid tumor mouse model. Administration of AME significantly decreased tumor size, induced apoptosis, and regulated key apoptotic markers, including p53, Bax, and caspase-3. Additionally, anti-inflammatory effects were observed through the suppression of TNFα expression, highlighting its potential as an anticancer adjuvant [26].

Curcumin Supplementation in AOM-DSS Mouse Model:

Curcumin, a well-known *Curcuma longa*, has been investigated for its chemopreventive effects in a high-protein diet (HPD)-fed, AOM-DSS-induced mouse model of CRC. Treatment with Curcumin led to a significant reduction in tumor multiplicity, attenuation of colonic inflammation, suppression of colonocyte proliferation, and decreased production of toxic metabolites. These findings support its role as a dietary chemopreventive agent, particularly in populations with high-risk dietary patterns [27].

Table 2. In vivo studies on anti-tumor effects of natural products in colorectal cancer animal models.

Natural products	Study type	Animal model	Key mechanism/findings	Author
Ferula hermonis (FHRH extract)	In vivo	DMBA-induced mammary tumor model (rodent)	Induced apoptosis, reduced tumor size, identified bioactive compounds (Alpha-Bisabolol, Baccatin III)	Abutaha, N., Nasr;2019
Ferula assa-foetida (OGR extract)	In vivo	HT-29 xenograft mouse model	Reduced tumor volume and induced apoptosis via PUMA, BIM, BIK, BAK upregulation	Elarabany, N.,2023
Arthrocnemum machrostachyum (AME extract)	In vivo	Ehrlich solid tumor (EST) model in mice	Induced apoptosis, reduced tumor size, modulated apoptotic gene expression	Sharawi, Z.W., 2020
Curcumin (*Curcuma longa*)	In vivo	AOM-DSS-induced CRC in high-protein diet-fed mice	Reduced tumor multiplicity, decreased inflammation, colonocyte proliferation, and toxic metabolites	Byun, S.-Y., 2015

4. Synthetic Compounds and Their Application

Recent advancements in colorectal cancer (CRC) research have highlighted the therapeutic potential of Synthetic and semi-synthetic compounds. These engineered molecules are specifically designed to target critical signaling pathways involved in CRC development, metastasis, and treatment resistance. Notably, synthetic compounds have demonstrated capabilities in inhibiting pathways such as EGFR, COX-2, and β-catenin, while also enhancing the efficacy of traditional chemotherapies.

4.1. In Vitro Study

Phenolic acid derivatives (C1-C4,P1-P4,G1-G4):

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A series of semi-synthetic derivatives originating from phenolic acids in Amaranthus *spinosus* have been developed to act as dual inhibitors of EGFR and COX-2. Among the synthesized compounds, C4 and G4 exhibited significant cytotoxic effects against HT-29 colorectal cancer cells, achieving IC_{50} values of 0.9 μM for EGFR and 0.5 μM for COX-2, respectively. These findings highlight their potential as dual-target inhibitors in CRC therapy [28].

Silver Nanoparticles from Chamomile Flower Extract (SN-CHM):

Biogenic synthesis of Silver nanoparticles (SN-CHM) using *Chamomile* flower extract has emerged as a novel anticancer approach. These nanoparticles exhibited stable morphology (~115 nm), negative surface charge, and antioxidant properties. In vitro studies demonstrated significant cytotoxicity against SW620 and HT-29 colorectal cancer cells, suggesting their potential as eco-friendly and effective anticancer agents [29].

Withaferin-A and 5-Fluorouracil Combination:

Combining withaferin-A (WA), a natural steroidal lactone, with 5-fluorouracil (5-FU) demonstrated enhanced anti-cancer efficacy in colorectal cancer cells. This combination effectively induced apoptosis through ER stress-mediated mechanisms, downregulated β-catenin signaling, and triggered G2/M cell cycle arrest. These results indicate a synergistic interaction, potentially overcoming resistance barriers in CRC treatment [30].

Myricetin-Conjugated Silver Nanoparticles:

The conjugation of the natural flavonoid *Myricetin* with silver nanoparticles has been explored for its enhanced cytotoxic effects against CRC cells. Characterization confirmed successful nanoparticle synthesis, with notable morphological changes and apoptosis observed in cancer cell lines. These findings suggest that nanotechnology-based delivery of myricetin may improve its therapeutic efficacy [31].

Adansonia digitata Polar Extract:

The polar extract of *Adansonia digitata* (baobab) fibers has been reported to possess significant anti-proliferative effects against HCT116 colorectal cancer and MCF-7 breast cancer cells. Mechanistic studies revealed its capacity to modulate gene expression linked to tumor growth suppression, marking it as a promising candidate for further exploration in CRC therapy [32].

Green-Synthesized Cobalt Oxide Nanoparticles:

Phytochemical synthesis of cobalt oxide nanoparticles using *Psidium guajava* leaf extract demonstrated potent anti-cancer effects against HCT116 colorectal and MCF-7 breast cancer cells, with minimal toxicity to normal cells. This suggests that green-synthesized nanoparticles could be effective, sustainable alternatives in CRC treatment [33].

Oxazole Derivatives:

A novel series of oxazole derivatives has shown anti-proliferative effects against HCT116 colorectal cancer cells, with compound 14 emerging as the most effective (IC_{50} = 71.8 μM). These findings indicate the therapeutic potential of oxazole analogs as novel anti-cancer agents [13].

Camptothecin-Encapsulated Nanocarriers (CEF):

To enhance its bioavailability and therapeutic effectiveness, *Camptothecin (CPT)* has been encapsulated within a cyclodextrin-EDTA-Fe_3O_4 (CEF) composite nanoparticle. This innovative formulation has demonstrated dose-dependent cytotoxicity against HT29 colorectal cancer cells, primarily through caspase-3-mediated apoptosis and G1 phase cell cycle arrest. The application of magnetic nanocarriers in this manner not only improves solubility but also enables targeted delivery, reducing systemic toxicity and enhancing anti-cancer efficacy [34].

Sipholenol A Derivatives for MDR Reversal:

The emergence of multidrug resistance (MDR) in colorectal cancer remains a significant therapeutic challenge. Semi-synthetic derivatives of *Sipholenol A*, including 4-O-acetate and 4-O-isonicotinate, have shown the ability to overcome P-glycoprotein-mediated MDR. These derivatives enhance intracellular drug accumulation by stimulating ATPase activity and displaying strong docking interactions with P-glycoprotein (P-gp), a key efflux transporter involved in

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chemoresistance. This highlights their potential as effective agents for reversing MDR in CRC and other cancers [35].

Table 3. In vitro studies of synthetic and semi-synthetic compounds in colorectal cancer treatment, with target cell lines and key outcomes.

Compound	Study type	Target cell lines (s)	Key findings	Author
C4, G4 (semi-synthetic derivatives)	In vitro	HT-29 (CRC), PaCa-2, A375, H-460, Panc-1	Dual EGFR and COX-2 inhibition; potent cytotoxicity	Abdelgawad, M.A., 2021
Silver nanoparticles using *Chamomile* (SN-CHM)	In vitro	SW620, HT-29 (CRC)	Induced apoptosis via BAX upregulation; reduced cell viability	Abdellatif, A. a. H., 2023
Withaferin-A + 5-FU (combination therapy)	In vitro	CRC cell lines (specific lines not detailed)	Induced ER stress-mediated apoptosis and autophagy; β-catenin inhibition; G2/M arrest	Alnuqaydan, A.M., 2020
Myricetin-conjugated silver nanoparticles	In vitro and In silico	CRC cell lines	Induced apoptosis; confirmed cytotoxicity; supported by TCGA analysis	Anwer, S.T., 2022
Polar extract of *Adansonia digitata* fibers	In vitro	HCT116 (CRC), MCF-7	Inhibited proliferation; modulated gene expression including CSNK2A3 and FGD3	El-Masry, O.S., 2021
Cobalt oxide nanoparticles (green synthesis from *Psidium guajava*)	In vitro	HCT116 (CRC), MCF-7	Reduced cancer cell viability; antibacterial and photocatalytic properties	Govindasamy, R., 2022
Oxazole analogues (compound 14)	In vitro	HCT116 (CRC)	Antiproliferative activity (IC_{50} = 71.8 μM); strong CDK8 binding (molecular docking)	Kakkar, S., 2018
Camptothecin-CEF nanocomposite	In vitro	HT29 (CRC), A549	Improved CPT delivery; induced apoptosis via	Krishnan, P., 2017

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			caspase-3; G1 phase arrest	
Sipholenol A-4-O-acetate, Sipholenol A-4-O-isonicotinate	In vitro	P-gp-overexpressing cancer cell lines	Reversed MDR by inhibiting P-gp efflux; increased paclitaxel retention	Zhang, Y., 2015

4.2. In Vivo Study

To evaluate the translational potential of synthetic compounds in colorectal cancer (CRC) therapy, several in vivo models have been employed to investigate their efficacy, mechanisms of action, and impact on tumor progression. The following studies highlight key findings that underscore their promise in CRC treatment.

[V4Q5]dDAVP in Combination with 5-FU:

[V4Q5]dDAVP, a synthetic analog of vasopressin targeting AVPR2 receptors, has been studied for its ability to enhance the anticancer effects of low-dose 5-fluorouracil (5-FU) in colorectal cancer models. In both CT-26 murine and COLO-205 human xenografts, the combination therapy significantly inhibited tumor growth, promoted apoptosis, and reduced lung metastasis. Mechanistically, this enhancement was linked to increased expression of p21 and p53, suggesting that [V4Q5]dDAVP could be an effective co-adjuvant in CRC therapy [36].

Zotarolimus as a Co-Adjuvant Therapy:

Zotarolimus, a semi-synthetic inhibitor of the mammalian target of rapamycin (mTOR), demonstrated marked anti-tumor effects in HCT-116 colorectal cancer xenograft models. When administered alone or in combination with 5-FU, it led to significant reductions in tumor volume and enhanced apoptotic signaling through cleaved caspase-3 and ERK pathways. Additionally, it downregulated key inflammatory and metastasis-associated proteins, highlighting its potential as a co-adjuvant in CRC management [37].

IMF-8 (Iminoflavone Derivative):

IMF-8, a semi-synthetic derivative of iminoflavone, has been evaluated for its chemopreventive properties in a DMH-induced colorectal cancer rat model. Its administration resulted in a reduction of aberrant crypt foci, a decrease in polyp formation, and the modulation of oxidative stress markers such as catalase and GSH. Furthermore, it downregulated pro-inflammatory cytokines (TNF-α, IL-6), indicating its protective role in CRC prevention [38].

WNT974 and Artesunate (ART) Combination Therapy:

The combination of WNT974, a porcupine inhibitor, with artesunate (ART), a semi-synthetic artemisinin derivative, demonstrated significant anti-cancer activity in CRC xenograft models. This therapeutic pairing promoted the degradation of KRAS via the ubiquitin-proteasome pathway, upregulated E3 ligases (ANAPC2, β-TrCP), and inhibited PI3K/Akt/mTOR signaling. These findings position the dual therapy as a promising strategy for targeting KRAS-driven colorectal cancers [39].

Potassium Koetjapate (KKA):

Potassium koetjapate (KKA), a semi-synthetic derivative of koetjapic acid, showed substantial anti-tumor activity in HCT116 colorectal cancer models. KKA was found to suppress tumor progression by downregulating anti-apoptotic markers (HSP60, Bcl-2, IGF-1) and upregulating apoptotic pathways through caspase activation and TRAIL receptors. Additionally, it inhibited key signaling pathways, including MAPK, Notch, and Wnt, indicating its multi-targeted mechanism in CRC treatment [40].

20(S)-Protopanaxadiol (PPD):

20(S)-Protopanaxadiol (PPD), a metabolite of ginsenosides, has demonstrated robust anti-cancer effects in HCT116 xenograft models. Treatment with PPD significantly reduced tumor volume and cell proliferation by inhibiting NF-κB, JNK, and MAPK/ERK pathways. Further mechanistic studies

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revealed its ability to downregulate PITPNA and upregulate AKAP8L, highlighting its potential as a multi-targeted therapeutic agent in CRC [41].

Table 4. In vivo evaluation of synthetic compounds in animal models for colorectal cancer, including tumor inhibition and molecular effects.

Compound	Study type	Animal model	Key findings	Author
[V4Q5]dDAVP + 5-FU	In vivo	CT-26 and COLO-205 tumor-bearing mice	Enhanced 5-FU efficacy; inhibited tumor growth and metastasis; increased survival	Sobol, N.T., 2023
Zotarolimus ± 5-FU	In vivo	HCT-116 xenograft in BALB/c nude mice	Reduced tumor growth; enhanced apoptosis; downregulated EGFR, COX-2, VEGF	Chang, G.-R., 2021
IMF-8 (semi-synthetic iminoflavone)	In vivo	DMH-induced CRC in rats	Reduced ACFs and inflammation; increased antioxidant enzymes	Prasad, V.G., 2014
WNT974 + Artesunate (ART)	In vivo	CRC xenograft mouse model	Promoted KRAS degradation; suppressed PI3K/Akt/mTOR; enhanced antitumor effect	Gong, R.-H., 2022
Potassium koetjapate (KKA)	In vivo	HCT116 xenograft in nude mice	Induced apoptosis via TRAILR-caspase axis; suppressed tumor growth and metastasis	Jafari, S.F., 2024
20(S)-Protopanaxadiol (PPD)	In vivo	HCT116 xenograft in nude mice	Inhibited tumor growth; suppressed NF-κB, JNK, MAPK/ERK; regulated PITPNA, AKAP8L	Gao, J.-L., 2013

5. Clinical Application

The clinical management of colorectal cancer (CRC) remains a significant challenge due to its high recurrence rates and resistance to conventional chemotherapy. To address these challenges, research has increasingly focused on both natural products and synthetic compounds that

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demonstrate promising anticancer properties. These therapeutic agents not only exhibit potent anti-tumor activity in preclinical models but also hold potential for translation into clinical settings.

5.1. Natural Products in Clinical Applications

Natural products have long been integral to cancer drug development due to their broad biological activities and minimal toxicity profiles. In Saudi Arabia, extensive research has been conducted on plant-derived extracts such as *Nigella sativa*, *Moringa oleifera*, *Ferula hermonis*, *Curcuma longa*, and *Rhazya stricta* for their anti-CRC properties.

For instance, *Nigella sativa* demonstrated the ability to modulate apoptotic pathways and suppress NF-κB and AP-1 signaling, making it a potential adjunctive therapy for CRC management [7]. *Moringa oleifera* extracts collected from the Saudi Arabian region exhibited significant apoptosis induction and cell cycle arrest in HCT-8 cells, supporting its use as a complementary treatment option [11].

The therapeutic potential of marine-derived chemicals, such as L-glutaminase from Halomonas meridiana, represents a novel clinical approach by denying cancer cells of vital nutrients like L-glutamine [12].

Similarly, silver nanoparticles derived from Lasiurus scindicus and Panicum turgidum showed robust anti-proliferative activity against HCT116 cells, demonstrating the potential of nanoparticle-based natural products to improve chemotherapeutic efficacy [18].

5.2. Synthetic Compounds and Clinical Relevance

Synthetic and semi-synthetic chemicals have emerged as significant players in CRC therapy, targeting specific cancer pathways and improving therapeutic outcomes. Compounds such as C4 and G4, dual inhibitors of EGFR and COX-2, have demonstrated considerable suppression of CRC cell growth [28]. The combination of Withaferin-A and 5-FU was found to eliminate chemoresistance via ER stress-mediated apoptosis, whilst oxazole derivatives effectively targeted CDK8 in HCT116 cells, suggesting a novel class of anti-cancer medicines [30]. In vivo models have proven the therapeutic promise of synthetic drugs such as Zotarolimus, a semi-synthetic mTOR inhibitor, and V4Q5dDAVP, which improved 5-FU efficacy in CRC-bearing mice by inhibiting tumor growth and metastasis [36].

Potassium koetjapate (KKA) and 20(S)-Protopanaxadiol (PPD) inhibited tumors via apoptosis induction and pathway modification, indicating their potential as therapeutic candidates [40]. Furthermore, the combination of WNT974 and artesunate (ART) successfully degraded KRAS protein in CRC animals, targeting one of the most difficult targets in colorectal cancer treatment [39].

These findings imply that synthetic and semi-synthetic drugs not only improve chemotherapy efficacy but also have distinct mechanisms of action that target cancer-specific pathways, easing their transition to clinical testing.

5.3. Translation to Clinical Settings

While preclinical discoveries are intriguing, the translation of these natural and synthetic medicines to clinical settings requires careful examination. Clinical trials that test their safety, effectiveness, and appropriate dose are crucial to establish their therapeutic advantages.

In Saudi Arabia, focusing more on clinical trials for plant-derived medicines and synthetic analogs could pave the way for new CRC therapeutics, perhaps lowering the burden of chemotherapy resistance and improving patient outcomes.

Furthermore, nanotechnology-based delivery systems are emerging as revolutionary platforms for improving the bioavailability and targeted distribution of these medicines, hence increasing their clinical utility. Combining these novel medicines with existing treatment methods has the potential to alter CRC management and increase patient survival rates.

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6. Limitation

While this study provides a thorough assessment of natural products and synthetic analogs for the treatment of colorectal cancer (CRC), some limitations must be addressed. While this study provides a comprehensive evaluation of natural products and synthetic analogs for colorectal cancer (CRC), some limitations must be addressed. This gap limits our capacity to generalize the therapeutic efficacy and safety of these drugs in human populations. Furthermore, while natural products such as Nigella sativa, Moringa oleifera, and marine-derived chemicals have shown promising anticancer effects, low bioavailability, poor solubility, and metabolic instability restrict their therapeutic utility.

Furthermore, the efficacy of many of the synthetic drugs mentioned, such as Withaferin-A, Zotarolimus, and Potassium koetjapate (KKA), is predicated on animal models and has yet to be verified in large-scale human clinical studies. This raises issues about translation to clinical practice because of differences in metabolism and medication response between animals and humans. Another major restriction is the scarcity of long-term safety data for many of these drugs, making it impossible to foresee any adverse effects or toxicities that may occur over prolonged use.

Furthermore, while the review emphasizes significant research contributions from Saudi Arabia in exploring plant-derived and marine bioactives, there is a lack of standardization in extraction methods, dosages, and formulations across studies, complicating the replication of results and the development of unified therapeutic guidelines. Finally, the study does not examine the potential pharmacokinetic interactions that may occur when these natural and synthetic medicines are taken in conjunction with traditional chemotherapy, which could affect both efficacy and safety outcomes.

Addressing these limitations through well-structured clinical trials, standardized extraction and packaging techniques, and extensive pharmacokinetic research is critical for moving these medicines from preclinical promise to clinical reality. Future research should focus not only on the discovery of potent anti-CRC drugs but also on their delivery, bioavailability, and clinical safety to maximize their potential as viable therapeutic choices for CRC patients in Saudi Arabia and around the world.

7. Future Directions

The promising preclinical outcomes of natural products and synthetic drugs in colorectal cancer (CRC) therapy indicate the need for a strategic shift toward clinical validation and therapeutic optimization. Future research should focus on well-designed clinical trials to assess the safety, efficacy, and optimal dose of these medicines in human populations. While in vitro and in vivo studies give strong evidence of anticancer effectiveness, converting these discoveries into therapeutic success necessitates overcoming several difficulties, including bioavailability, pharmacokinetic variability, and possible toxicity.

To improve therapeutic application, nanotechnology-based delivery systems for natural compounds, including Nigella sativa, Moringa oleifera, and Curcuma longa, could considerably improve bioavailability and target specificity. Nanocarriers, liposomes, and polymeric nanoparticles are novel techniques for improving therapeutic stability, protecting bioactive molecules from degradation, and selectively delivering them to tumor locations while limiting systemic toxicity [14,15].

Furthermore, combinatorial therapy including synthetic drugs like Zotarolimus, Potassium koetjapate (KKA), and 20(S)-Protopanaxadiol (PPD) alongside conventional chemotherapeutics have promise for overcoming resistance mechanisms and boosting synergistic benefits [37,40,41].

Furthermore, studying biomarker-based customized medicine could help identify individuals who are most likely to benefit from natural or synthetic compound-based medicines. Biomarkers for predicting therapeutic response, such as KRAS mutation status, EGFR expression, and COX-2 levels, can help guide personalized treatment plans that maximize efficacy while minimizing side effects. Saudi Arabia, with its distinct biodiversity, is well-positioned to lead research in plant-derived and marine bioactives, utilizing its natural resources for drug discovery and development [42–44].

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Collaboration among academic institutions, pharmaceutical corporations, and clinical research institutes is critical for accelerating the development of these innovative drugs. International collaborations can improve resource sharing, standardize clinical protocols, and speed up the approval process for innovative CRC treatments. Furthermore, establishing biobanks and cancer registries in Saudi Arabia could allow for more robust population-based studies, providing deeper insights into CRC epidemiology and response to innovative treatments. Future research should also look at the long-term safety profiles of these natural and synthesized substances, including longitudinal studies and post-marketing surveillance to determine their impact on survival rates and quality of life. Addressing these research gaps will pave the way for new, more effective, and safer therapies for CRC patients, thereby significantly lowering cancer mortality rates in Saudi Arabia and elsewhere.

8. Conclusion

Colorectal cancer (CRC) is a major global health concern due to its high incidence, treatment resistance, and spreading potential. Over the last decade, advances in understanding the molecular biology of CRC have paved the door for new therapy methods that combine natural products and synthetic chemicals. Plant-derived bioactives such as Nigella sativa, Moringa oleifera, and Curcuma longa have demonstrated promise anticancer effects, principally through apoptosis induction, oxidative stress regulation, and inhibition of cancer cell proliferation. Meanwhile, marine bioactives and synthetic analogs are emerging as effective therapeutic agents, improving the efficacy of standard chemotherapies and targeting CRC cells.

Nanocarriers, liposomes, and polymeric nanoparticles are being investigated as vehicles to selectively deliver these bioactives to tumor sites, maximizing therapeutic impact while minimizing adverse effects. The development of nanotechnology-based delivery systems has further revolutionized the clinical application of these compounds by increasing their bioavailability, targeting specificity, and minimizing systemic toxicity [14,15].

Biomarkers such as KRAS mutation status, EGFR expression, and COX-2 levels are proven to be important in directing customized treatment regimens, allowing doctors to predict therapeutic responses and modify therapies appropriately. These developments contribute to a trend toward precision medicine in CRC care, which improves patient outcomes through personalized therapeutic regimens [42–44].

Despite substantial advances, there are still barriers to transferring preclinical triumphs into mainstream clinical use. Future research should concentrate on large-scale clinical trials, standardized formulations, and a more in-depth examination of combination medicines to overcome resistance mechanisms. Furthermore, establishing biobanks and cancer registries in countries such as Saudi Arabia could improve population-based research and speed up the development of localized therapy methods.

In conclusion, the integration of natural products, marine bioactives, synthetic compounds, and nanotechnology-based delivery systems represents a promising frontier in colorectal cancer therapy. These innovations, when combined with predictive biomarkers and personalized medicine approaches, have the potential to redefine CRC treatment paradigms, offering hope for improved survival rates and quality of life for patients worldwide.

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