INDONESIAN NATURAL COMPOUNDS AS POTENTIAL ANTI-COLORECTAL CANCER AGENTS: A SYSTEMATIC REVIEW

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Abstract

Colorectal cancer (CRC) remains a major global health burden, with increasing incidence and mortality worldwide, including in Indonesia. Natural products have long been recognized as a valuable source of anticancer agents, yet many studies on Indonesian natural resources focus on crude extracts rather than isolated compounds with defined mechanisms of action. This study aimed to systematically review isolated natural compounds derived from Indonesian biological sources with reported anti-colorectal cancer activity. A systematic review was conducted following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines, with literature searches performed in PubMed, SpringerLink, and ScienceDirect. Eligible studies included original experimental research investigating isolated compounds against CRC models with quantitative outcomes. A total of 16 studies were included, identifying diverse compounds from terrestrial plants, marine organisms, and propolis. Several compounds demonstrated potent cytotoxic activity, particularly in the low micromolar range, and were associated with apoptosis induction and cell cycle arrest. Mechanistic analysis revealed involvement of caspase-dependent pathways, NF-κB inhibition, and ROS-mediated apoptosis. However, many studies lacked detailed mechanistic validation and in vivo evidence. Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) profiling indicated generally favorable pharmacokinetic properties, although potential toxicity risks and variability in absorption were observed. Overall, Indonesian natural compounds represent promising candidates for CRC therapy, but further studies are needed to improve mechanistic understanding, validate efficacy in vivo, and assess pharmacokinetic and safety profiles.

Keywords: *Colorectal cancer, Indonesian natural products, Isolated compounds, Anticancer activity; ADMET profiling.*

Introduction

Colorectal cancer (CRC) is a major global health burden, ranking as the third most commonly diagnosed malignancy and the second leading cause of cancer-related death worldwide, with an estimated 1.9–1.93 million new cases and about 0.9–0.94 million deaths in 2020 (Morgan et al., 2023; Sung et al., 2021). The global number of CRC cases is projected to rise to approximately 3.2 million new cases and 1.6 million deaths by 2040, driven largely by population ageing, growth, and the westernization of lifestyles in low- and middle-income countries (Morgan

et al., 2023; Xi and Xu, 2021). In Indonesia, cancer is the third leading cause of mortality, with GLOBOCAN estimates indicating around 396,914–408,661 new cancer cases and 234,511–242,099 cancer deaths in 2020–2022, among which colorectal cancer is consistently listed among the top causes of cancer incidence and mortality (Andinata et al., 2023; Ministry of Health of the Republic of Indonesia, 2022). More detailed analyses show that CRC incidence in Indonesia has increased sharply, reaching approximately 12.8 cases per 100,000 adults and contributing substantially to catastrophic health expenditures under the national health insurance scheme (Purnomo et al., 2023).

Although multimodal treatment (including surgery, chemotherapy, radiotherapy, targeted agents, and, in selected subsets, immunotherapy) has improved survival, chemotherapy and targeted regimens remain limited by systemic toxicity, suboptimal response rates, and the rapid development of intrinsic and acquired resistance that contribute to recurrence and poor long-term outcomes (Yao et al., 2021). These limitations underscore the need for safer and more effective therapeutic options, including novel agents that can circumvent resistance mechanisms and reduce medication-related harms in patients with CRC.

Natural products have long played a central role in anticancer drug discovery, providing structurally diverse scaffolds and pharmacophores that have led to clinically important agents such as paclitaxel, vincristine, and camptothecin derivatives (Atanasov et al., 2021; Huang et al., 2021). Recent reviews highlight that natural products and their semi-synthetic analogues continue to contribute substantially to the oncology pharmacopeia, offering multi-targeted mechanisms, such as modulation of apoptosis, oxidative stress, angiogenesis, epigenetic regulation, and immune responses, that are particularly relevant for complex diseases like CRC (Huang et al., 2021; Safe et al., 2024; Roy et al., 2025). Indonesia, as one of the world's megabiodiversity hotspots, harbours an estimated tens of thousands of plant species, with approximately 6,000 traditionally used as medicinal plants, positioning the archipelago as a "natural laboratory" for bioprospecting anticancer agents (Rani et al., 2023).

Several narrative and systematic reviews have catalogued Indonesian medicinal plants with in vitro anticancer activity across various tumour types, including breast, cervical, lung, and colon cancers, and have identified numerous promising taxa such as Annona muricata, Zingiber species, Dendrophthoe pentandra, and Myrmecodia pendans (Alhawaris et al., 2023; Permatasanti and Hidayat, 2023). However, much of this work has focused predominantly on crude or semi-purified extracts rather than fully characterized isolated constituents, and many studies have assessed general cytotoxicity across multiple cancer cell lines without specific emphasis on colorectal cancer models (Permatasanti and Hidayat, 2023).

Although a growing global literature describes plant-derived bioactive compounds with anti-colorectal activity, most comprehensive reviews synthesize data without a specific geographic focus or treat Indonesian resources only tangentially (Dong et al., 2022). At the same time, a landmark systematic review by Illian et al. (2021) summarized the "current status, distribution, and future directions" of natural products against colorectal cancer in Indonesia, demonstrating that many Indonesian-derived natural products exhibit cytotoxicity against CRC cell lines such as WiDr, HT-29, and HCT-116, and that terpenoids, phytosterols, phenolics, alkaloids, and polyisoprenoids constitute the dominant chemical classes.

Nevertheless, that and related Indonesian reviews primarily catalogue cytotoxic findings and distribution patterns of natural products, often aggregating data from crude extracts and partially purified fractions, with limited critical appraisal of evidence focused strictly on fully isolated compounds and their mechanistic profiles against CRC. Furthermore, existing syntheses on Indonesian medicinal plants generally span multiple cancer types and do not provide a dedicated, methodologically rigorous, colorectal cancer–specific evidence synthesis that systematically evaluates the strength, reproducibility, and translational relevance of isolated natural compounds from Indonesian biodiversity (Illian et al., 2021). This fragmentation of the literature and the lack of a focused, high-quality synthesis on isolated Indonesian-derived

constituents with anti-colorectal activity highlight a critical knowledge gap that can be addressed through a structured systematic review.

Therefore, the present study aims to conduct a systematic review to comprehensively identify and critically evaluate isolated natural compounds derived from Indonesian biological resources (plants, marine organisms, and other natural sources) that have been investigated for anti-colorectal cancer activity in vitro and/or in vivo. Specifically, this review will: (i) catalogue Indonesian-origin isolated compounds tested against colorectal cancer models; (ii) assess the magnitude and robustness of their anticancer effects, including cytotoxicity, antiproliferative activity, apoptosis induction, cell cycle modulation, anti-metastatic properties, and impacts on tumour microenvironment or immune modulation; and (iii) synthesize reported molecular targets and pathways to elucidate putative mechanisms of action in the context of CRC.

Methods

Study Design and Protocol

This study was conducted as a systematic review following the PRISMA 2020 guidelines. The review aimed to identify isolated natural compounds derived from Indonesian biological sources with reported anti-colorectal cancer (CRC) activity. The study protocol was conceptually structured prior to data collection to ensure transparency and reproducibility.

Eligibility Criteria

Eligibility criteria were defined using a preclinical-oriented PICOS framework (Table 1). Briefly, the population included human CRC cell lines and in vivo CRC models. The intervention comprised isolated or purified compounds derived from Indonesian natural products, including terrestrial and marine sources. Studies involving crude extracts, fractions, or nanoparticle-based formulations were excluded. Eligible studies were required to report at least one quantitative anticancer outcome, such as IC50, apoptosis induction, cell cycle arrest, or tumor reduction. Only original experimental studies were included.

Table 1. Eligibility criteria defined using a preclinical-oriented PICOS framework for the selection of studies investigating isolated Indonesian natural compounds with anti-colorectal cancer activity.

Component	Inclusion Criteria	Exclusion Criteria
Population (P)	Human colorectal cancer cell lines and in vivo CRC models	Non-colorectal cancer models
Intervention (I)	Isolated or purified compounds derived from Indonesian natural products (terrestrial plants, marine organisms, or associated microorganisms)	Crude extracts, fractions, mixtures, or nanoparticle-based formulations
Comparator (C)	Untreated control, vehicle control, or standard chemotherapeutic agents	Studies without a comparator or control group
Outcome (O)	Quantitative anticancer outcomes, including IC50/cell viability, apoptosis induction, cell cycle arrest, tumor volume reduction, or molecular target modulation	Studies without quantitative outcomes
Study Design (S)	Original experimental studies	Reviews, editorials, conference abstracts, and non-research articles

Search Strategy

A comprehensive literature search was performed across multiple electronic databases, including PubMed, SpringerLink and ScienceDirect, from inception until the latest available date. The search strategy combined controlled vocabulary and free-text terms related to colorectal cancer, Indonesian natural products, and isolated compounds. Representative keywords included:

"colorectal cancer" OR "colon cancer" AND "Indonesia" OR "Indonesian" AND "isolated compound" OR "phytochemical" AND "cytotoxic" OR "apoptosis". The search was adapted to the syntax of each database. Reference lists of relevant articles were also manually screened to identify additional eligible studies.

Study Selection

All retrieved records were imported into a reference management software, and duplicates were removed. Two independent reviewers screened titles and abstracts based on predefined eligibility criteria. Full-text articles were then assessed for final inclusion. Discrepancies were resolved through discussion or consultation with a third reviewer. The study selection process was documented using a PRISMA flow diagram.

Data Extraction

Data were extracted independently by two reviewers using a standardized extraction form. Extracted variables included study identification (author and year), biological source (plant or marine organism), plant part or material, compound name, experimental model, IC50 values, apoptosis induction, cell cycle arrest, molecular targets, signaling pathways, comparator drugs, and key findings. When data were missing or unclear, they were recorded as "not reported" to maintain transparency.

Risk of Bias Assessment

The risk of bias of included studies was assessed using an adapted approach based on the Toxicological Data Reliability Assessment Tool (ToxRTool). Each study was evaluated across five domains, including clarity of experimental design, dose–response reporting, reproducibility, validity of outcome measurement, and mechanistic evidence. Studies were categorized as having low, moderate, or high risk of bias based on the number of fulfilled criteria.

Data Synthesis

A qualitative synthesis was performed due to heterogeneity in experimental designs, compound types, and outcome reporting. Compounds were compared based on their cytotoxic potency, mechanistic evidence, and experimental models. Where appropriate, findings were grouped by chemical class and biological pathways to identify trends and research gaps.

ADMET Profiling

To complement the experimental findings, an in silico ADMET profiling was conducted for all identified compounds. Molecular structures of the compounds were obtained from public chemical databases such as PubChem (https://pubchem.ncbi.nlm.nih.gov/) in SMILES format. These structures were then analyzed using the DeepPK (https://biosig.lab.uq.edu.au/deeppk) platform, a deep learning-based tool for pharmacokinetic prediction.

Key ADMET parameters evaluated included oral bioavailability, Caco-2 permeability values, blood–brain barrier permeability, plasma protein binding, clearance, and toxicity-related endpoints. The predicted results were interpreted qualitatively to assess the drug-likeness and pharmacokinetic feasibility of each compound. Compounds with favorable ADMET profiles were considered potential candidates for further drug development.

Result and Discussion

Study Characteristics

This systematic review identified and synthesized evidence on isolated natural compounds derived from Indonesian biological sources with reported anti-colorectal cancer activity. Following a structured selection process based on predefined eligibility criteria, a total of included studies were analyzed. The characteristics of the included studies, including biological sources, compound types, and experimental models, are summarized in Table 2. Overall, the identified compounds represent diverse chemical classes and exhibit varying degrees of cytotoxic activity and mechanistic evidence. The results are presented in terms of study characteristics, anticancer

activity, mechanistic insights, and risk of bias assessment. A total of 16 studies met the inclusion criteria, encompassing isolated natural compounds derived from Indonesian biological sources, including terrestrial plants, marine organisms, and propolis-derived products, the study selection process is illustrated in Figure 1.

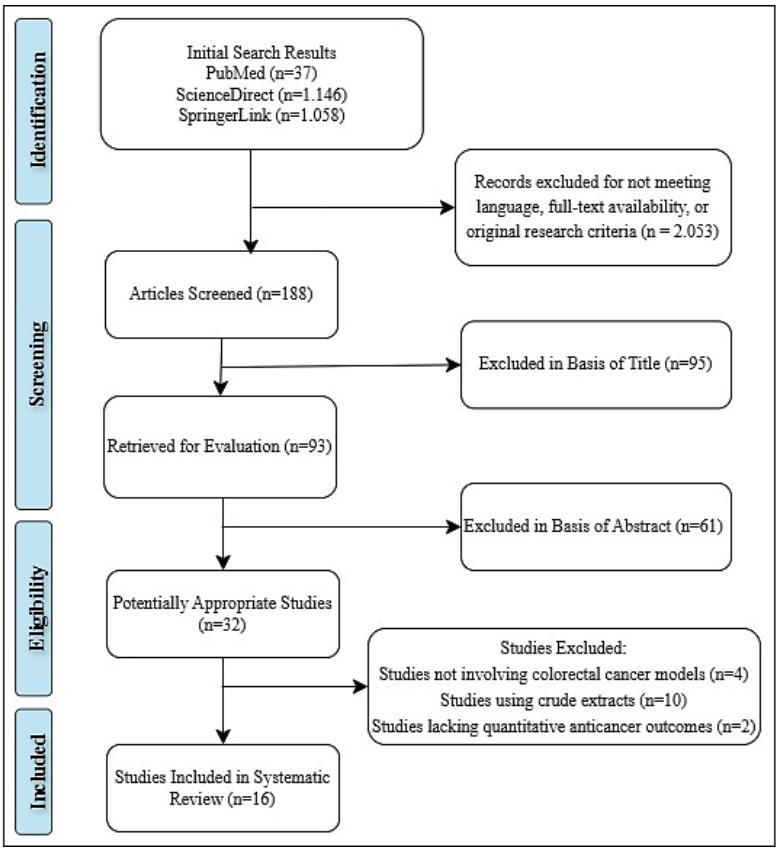

Figure 1. PRISMA 2020 flow diagram illustrating the study selection process, including identification, screening, eligibility, and inclusion of studies in this systematic review.

The majority of studies employed in vitro CRC cell lines, particularly HT-29, HCT116, and WiDr, with limited in vivo validation. The identified compounds represented diverse chemical classes, including xanthones (α-mangostin, garcinone D), phenolic compounds (protocatechuic acid), terpenoids (cycloartane), alkaloids (aaptamine), and polyketides (oxisterigmatocystins). Marine-derived compounds and fungal metabolites were also included, reflecting the diversity of Indonesian natural products. The characteristics of the included studies, including biological sources, isolated compounds, and experimental models, are summarized in Table 2

Table 2. Characteristics of included studies describing the sources, isolated compounds, and colorectal cancer models used to evaluate the anticancer activity of Indonesian natural products.

Study ID	Source	Part / Material	Compound	CRC Models
(Ahmad et al., 2018)	*Polygonum minus*	Stem	Polygonumins A	HCT116
(Handayani et al., 2017)	*Caesalpinia sappan*	Heartwood	Brazilin	WiDr
			Brazilein	WiDr
(Yuliana et al., 2020)	*Oryza sativa* (black rice)	Bran	Protocatechuic acid	WiDr
(Kustiawan et al., 2015)	*Trigona incisa* propolis	Resin	Cardol (5-pentadecylresorcinol)	SW620

(Mutiah et al., 2018)	*Calotropis gigantea*	Root	Calotroposide A	WiDr
(Sari et al., 2018)	*Nypa fruticans*	Leaf	Polyisoprenoids (dolichol/polyprenol mixture)	WiDr
(Fadilah et al., 2023)	*Syzygium aromaticum*	Clove bud	4-[(2S)-2,3-dihydroxypropyl]-2-methoxyphenyl 2-hydroxybenzoate	HT-29
(Jiso et al., 2021)	*Haliclona* sp.	Whole sponge	Smenospongine	HCT116; HT-29
	Verongula rigida		Ilimaquinone	HCT116; HT-29
(Hardhiyuna et al., 2024)	*Aaptos suberitoides*	Whole sponge	Aaptamine	DLD-1
(Leong et al., 2016)	*Aglaia exima*	Leaf	Cycloart-24-ene-26-ol-3-one (Cycloartane)	HT-29; CaCo-2
(Illian et al., 2019)	*Avicennia alba*	Leaf	Polyisoprenoids (dolichols C60–C100)	WiDr
(Artasasta et al., 2021)	*Neopetrosia chaliniformis*	Fungal culture	Oxisterigmatocystin J	HT-29
			Oxisterigmatocystin K	HT-29
			Aspergillicin A	HT-29
(Han et al., 2009)	*Garcinia mangostana*	Stem bark	α-Mangostin	HT-29
			β-Mangostin	HT-29
			Garcinone D	HT-29
			3-Isomangostin	HT-29
			9-Hydroxycalabaxanthone	HT-29
(Kustiawan et al., 2017)	*Trigona incisa* propolis	Resin	Cardol (5-pentadecylresorcinol)	SW620
(Yoon et al., 2023)	*Curcuma longa*	Rhizome	Demethoxycurcumin	HCT116
(Li et al., 2023)	*Garcinia nobilis*	Fruit-derived compound	Garcinone E	HT-29; Caco-2

Cytotoxic Activity

The cytotoxic potency of the identified compounds varied substantially. Several compounds demonstrated strong anticancer activity, with IC50 values in the low micromolar range (<10 μM), including Aspergillicin A (1.7 μM); α-Mangostin (1.7 μM); Oxisterigmatocystin K (1.63 μM); Garcinone D (4.9 μM). In contrast, other compounds such as calotroposide A (180.2 μg/mL) and cycloartane (173.7 μg/mL) exhibited relatively weak cytotoxic effects. Notably, IC50 values were reported in mixed units (μM and μg/mL), reflecting differences in study design and reporting standards.

Apoptosis and Cell Cycle Regulation

Most compounds demonstrated the ability to induce apoptosis, suggesting a common anticancer mechanism. However, only a subset of studies provided detailed mechanistic insights. Cell cycle arrest was reported in several studies, primarily at the G0/G1 and G2/M phases, indicating disruption of cell proliferation pathways. For example Cardol induced G1 phase arrest, Calotroposide A induced S and G2/M arrest, and Cycloartane induced G2/M arrest. However, a considerable proportion of studies did not report cell cycle effects, limiting mechanistic interpretation. The cytotoxic activity and biological effects of the identified compounds are summarized in Table 3.

Table 3. Anticancer activity of isolated Indonesian natural compounds, including cytotoxic potency (IC50), apoptosis induction, cell cycle arrest, and comparator agents.

Compound	IC50	Apoptosis	Cell Cycle Arrest	Comparator
Polygonumins A	41 µM	Not reported	Not reported	Doxorubicin
Brazilin	52 µM	Yes	Yes	Cisplatin
Brazilein	8.53 µM	Yes	Yes	Cisplatin
Protocatechuic acid	4.51 µg/mL	Yes	Not reported	5-Fluorouracil
Cardol (5-pentadecylresorcinol)	17.23 µg/mL	Yes	G1 phase arrest	Doxorubicin
	~20–60 µM	Yes	G0/G1 phase arrest	Doxorubicin
Calotroposide A	180.2 µg/mL	Yes	S and G2/M phase arrest	Cisplatin
Polyisoprenoids (dolichol/polyprenol mixture)	26.56 µM	Yes	G0/G1 phase arrest	Doxorubicin
4-[(2S)-2,3-dihydroxypropyl]-2-methoxyphenyl 2-hydroxybenzoate	~6–10 µM	Yes	Not reported	Eugenol
Smenospongine	~10–15 µM	Yes	Sub-G1 accumulation	5-Fluorouracil
Ilimaquinone	9.5 µg/mL	Yes	Cell cycle arrest (unspecified phase)	5-Fluorouracil
Aaptamine	11.5 µM	Not reported	Not reported	Doxorubicin
Cycloartane (cycloart-24-ene-26-ol-3-one)	173.7 µg/mL	Yes	G2/M phase arrest	Cisplatin; 5-Fluorouracil
Polyisoprenoids (dolichols C60–C100)	6.28 µM	Yes	G0/G1 phase arrest	Doxorubicin
Oxisterigmatocystin J	15.14 µM	Yes	Not reported	Doxorubicin
Oxisterigmatocystin K	1.63 µM	Yes	Not reported	Doxorubicin
Aspergillicin A	1.7 µM	Yes	Not reported	Doxorubicin

α-Mangostin	1.7 µM	Yes	Not reported	Camptothecin
β-Mangostin	2.3 µM	Yes	Not reported	Camptothecin
Garcinone D	4.9 µM	Yes	Not reported	Camptothecin
3-Isomangostin	9.1 µM	Yes	Not reported	Camptothecin
9-Hydroxycalabaxanthone	4.51 µg/mL	Yes	Not reported	Camptothecin
Demethoxycurcumin	~5–20 µM	Yes	Not reported	Doxorubicin
Garcinone E	41 µM	Yes	Yes	N-acetylcysteine

Mechanistic Evidence

Mechanistic evidence varied across studies. High-quality studies demonstrated involvement of Caspase-dependent apoptosis pathways, ROS-mediated mitochondrial dysfunction, NF-κB inhibition (xanthone derivatives). Conversely, several compounds (aaptamine, oxisterigmatocystins) were evaluated primarily for cytotoxicity without detailed molecular target analysis. The molecular targets and signaling pathways associated with the identified compounds are summarized in Table 4.

Table 4. Molecular targets and signaling pathways associated with the anticancer activity of isolated Indonesian natural compounds against colorectal cancer.

Compound	Target Proteins	Signaling Pathways
Polygonumins A	Not reported	Not reported
Brazilin	Not reported	S-phase and G2/M cell cycle arrest
Brazilein	Not reported	S-phase and G2/M cell cycle arrest
Protocatechuic acid	p53; BAX; BCL-2; Caspase-1, -7, -8, -9	Intrinsic and extrinsic apoptosis; pyroptosis
Calotroposide A	Caspase-8	Extrinsic apoptosis pathway
Polyisoprenoids (dolichol/polyprenol mixture)	BCL-2; Cyclin D1	G0/G1 cell cycle arrest
4-[(2S)-2,3-dihydroxypropyl]-2-methoxyphenyl 2-hydroxybenzoate	BCL-2	BCL-2 inhibition pathway
Smenospongine	p53; p21; γH2AX; BAX; BIM; Caspase-9	DNA damage response and mitochondrial apoptosis
Ilimaquinone	p53; p21; CHK1; Caspase-9	DNA damage response pathway
Aaptamine	Not reported	Not reported
Cycloart-24-ene-26-ol-3-one (Cycloartane)	TNF-R1; Caspase-8; Caspase-9; Caspase-3/7; BID; Cytochrome c	TNF-R1-mediated extrinsic and intrinsic (mitochondrial) apoptosis
Polyisoprenoids (dolichols C60–C100)	COX-2	G0/G1 arrest and COX-2 suppression
Oxisterigmatocystin J	Not reported	Apoptosis induction
Oxisterigmatocystin K	Not reported	Apoptosis induction
Aspergillicin A	Not reported	Apoptosis induction

α-Mangostin	NF-κB (p50, p65)	NF-κB inhibition and cytotoxicity
β-Mangostin	NF-κB (p50)	NF-κB inhibition
Garcinone D	NF-κB (p65)	NF-κB inhibition
3-Isomangostin	Not reported	Cytotoxicity (mechanism not specified)
9-Hydroxycalabaxanthone	Not reported	Cytotoxicity (mechanism not specified)
Cardol (5-pentadecylresorcinol)	Caspase-3; Caspase-9; PARP; ROS; MMP	Mitochondrial apoptosis and ROS-dependent pathway
Demethoxycurcumin	p53; BAX; BCL-2; Caspase-3; Caspase-9	Apoptosis and metabolic reprogramming
Garcinone E	Caspase-3; Caspase-9; BCL-2; PARP	JNK signaling and ROS-mediated apoptosis

Risk of Bias Assessment

The risk of bias assessment is illustrated in Figure 2, revealed that most studies demonstrated low to moderate methodological quality. Studies classified as low risk generally reported clear experimental designs, dose–response relationships, and mechanistic insights. In contrast, high-risk studies were primarily characterized by limited reproducibility and lack of mechanistic evidence. These findings indicate variability in methodological quality across the included studies.

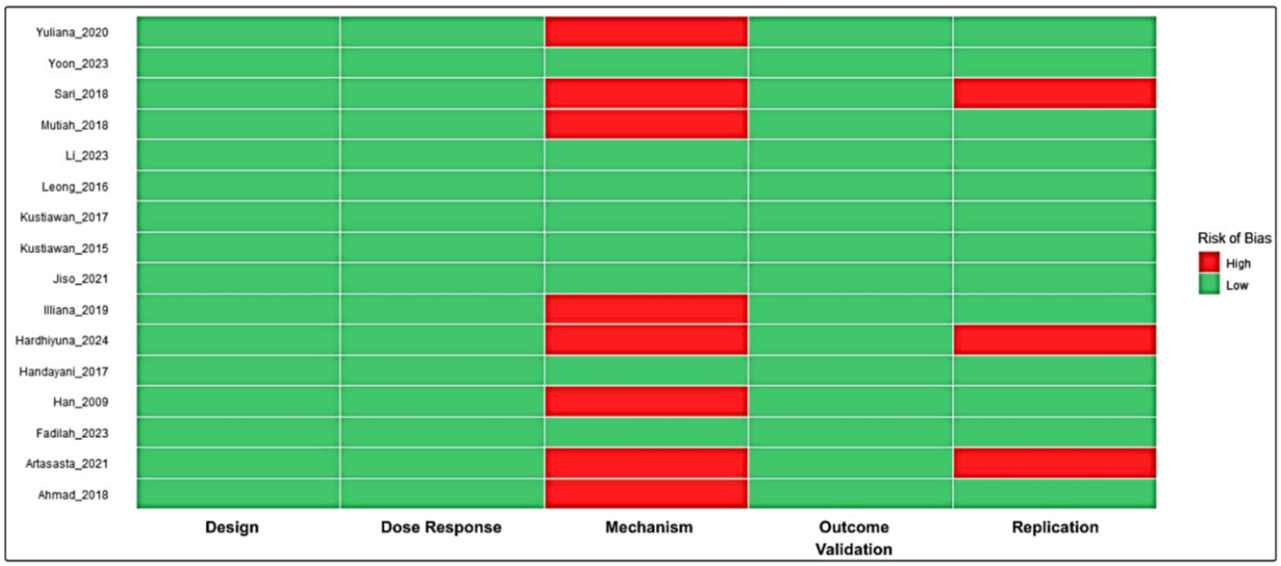

Figure 2. Risk of bias assessment of included studies using an adapted ToxRTool framework.

ADMET Profilling

The ADMET profiling results (Figure 3) indicate that the majority of the selected compounds exhibit moderate absorption characteristics, as reflected by their Caco-2 permeability values and favorable oral bioavailability predictions (F20 and F50). Notably, a substantial proportion of compounds were predicted to interact with P-glycoprotein, suggesting potential implications for drug efflux and bioavailability. In terms of metabolism, most compounds were identified as non-substrates and non-inhibitors of CYP3A4, indicating a relatively low risk of metabolic drug–drug interactions. The distribution profile revealed moderate plasma protein binding and limited blood–brain barrier penetration, which is generally desirable for colorectal cancer therapy to minimize central nervous system exposure. Excretion analysis showed

predominantly short half-lives with moderate clearance rates, suggesting the need for dosing optimization. However, toxicity predictions highlighted potential concerns, with a considerable proportion of compounds classified as hepatotoxic and AMES-positive, indicating possible safety risks. Overall, while several compounds demonstrate favorable pharmacokinetic properties, their toxicity profiles warrant further experimental validation to support their development as anticancer candidates.

Figure 3. In silico ADMET profiling of selected Indonesian natural compounds

Discussion

This systematic review demonstrates that Indonesian natural products represent a promising source of anti-colorectal cancer agents, with several compounds exhibiting potent cytotoxic activity in vitro. Notably, xanthone derivatives such as α-mangostin and garcinone D consistently showed strong activity, supporting their potential as lead compounds. However, the observed variability in potency highlights the need for careful prioritization of compounds for further development. Although apoptosis induction was commonly reported, mechanistic depth varied significantly. Only a subset of studies provided detailed insights into signaling pathways, such as caspase activation and NF-κB inhibition. This inconsistency suggests that many studies remain at a screening level, rather than advancing toward mechanism-based drug discovery. The lack of standardized mechanistic reporting limits cross-study comparisons and reduces translational relevance.

The findings of this review, particularly the cytotoxic potential of xanthone compounds and apoptosis-inducing agents in the low micromolar range, are consistent with previous reports demonstrating the in vitro anticancer activity of xanthones derived from *Garcinia* species (Han et al., 2009), although in vivo evidence for several xanthones remains limited. The observed apoptotic activity of oxisterigmatocystin derivatives in this study also supports findings by Artasasta *et al*. (2021), who reported apoptosis induction by marine-derived fungal metabolites.

Furthermore, the apoptosis mechanisms associated with mitochondrial disruption and oxidative stress observed for cardol align with the mechanistic analysis by Kustiawan *et al*. (2017), which highlighted the role of ROS-mediated mitochondrial pathways in colorectal cancer cells. More broadly, these results reinforce the well-established notion that natural products remain a rich source of chemical diversity for anticancer drug discovery (Newman and Cragg, 2020). Considering the persistent global burden of colorectal cancer (Sung et al., 2021) and the inconsistencies identified in this dataset, including variability in IC_{50} units, mechanistic depth, and limited in vivo validation, further systematic investigations are warranted. These should include in vivo validation, pharmacokinetic and ADMET studies, and standardized experimental reporting to facilitate the prioritization of promising compounds for future development.

A critical finding of this review is the limited availability of high-quality studies investigating isolated compounds from Indonesian sources specifically targeting colorectal cancer. Three major gaps were identified, Overreliance on cytotoxicity assays without mechanistic validation, Lack of in vivo studies and translational evidence, lastly Inconsistent reporting standards across studies. These gaps highlight the need for more comprehensive and standardized research approaches.

Conclusion

This systematic review highlights that isolated natural compounds derived from Indonesian biological resources exhibit promising anti-colorectal cancer activity, particularly through apoptosis induction and cell cycle modulation. Several compounds, especially xanthone derivatives and selected marine-derived metabolites, demonstrated potent cytotoxic effects in the low micromolar range and were supported by mechanistic evidence involving caspase activation, NF-κB inhibition, and ROS-mediated pathways. However, the overall evidence remains limited by variability in methodological quality, insufficient mechanistic depth, and the scarcity of in vivo validation. Additionally, ADMET profiling revealed that although many compounds possess favorable pharmacokinetic properties, potential toxicity concerns and suboptimal permeability may limit their translational potential. Therefore, further well-designed studies incorporating standardized reporting, in vivo validation, and comprehensive pharmacokinetic evaluation are required to support the development of these compounds as potential therapeutic agents for colorectal cancer

Daftar Pustaka

Ahmad, R., Sahidin, I., Taher, M., Low, C., Noor, N.M., Sillapachaiyaporn, C., Chuchawankul, S., Sarachana, T., Tencomnao, T., Iskandar, F., Rajab, N.F., Baharum, S.N., 2018. Polygonumins A, a newly isolated compound from the stem of Polygonum minus Huds with potential medicinal activities. Sci Rep 8, 4202. https://doi.org/10.1038/s41598-018-22485-5

Alhawaris, A., Dengen, N., Budiman, E., Widians, J.A., Wati, M., Hairah, U., Ugiarto, M., 2023. Potency of Borneo endemic and typical plants as anti-cancer medicines. Jurnal Kimia dan Pendidikan Kimia.

Andinata, B. et al., 2023. A comparison of cancer incidences between Dharmais Cancer Hospital and GLOBOCAN 2020. Indonesian Journal of Cancer 17.

Artasasta, M.A., Yanwirasti, Y., Taher, M., Djamaan, A., Ariantari, N.P., Edrada-Ebel, R.A., Handayani, D., 2021. Apoptotic Activity of New Oxisterigmatocystin Derivatives from the Marine-Derived Fungus Aspergillus nomius NC06. Mar Drugs 19. https://doi.org/10.3390/md19110631

Atanasov, A.G., Zotchev, S.B., Dirsch, V.M., Taskforce, I.N.P.S., 2021. Natural products in drug discovery: advances and opportunities in the multi-omics era. Nature Reviews Drug Discovery.

Dong, J. et al., 2022. Can natural products be used to overcome the limitations of colorectal cancer treatment? Frontiers in Oncology 12, 884423.

Fadilah, F., Andrajati, R., Arsianti, A., Paramita, R.I., Erlina, L., Istiadi, K.A., Yanuar, A., 2023. Synthesis and in vitro Activity of Eugenyl Benzoate Derivatives as BCL-2 Inhibitor in Colorectal Cancer with QSAR and Molecular Docking Approach. Asian Pac J Cancer Prev 24, 2973–2981. https://doi.org/10.31557/APJCP.2023.24.9.2973

Han, A.-R., Kim, J.-A., Lantvit, D.D., Kardono, L.B.S., Riswan, S., Chai, H., Carcache de Blanco, E.J., Farnsworth, N.R., Swanson, S.M., Kinghorn, A.D., 2009. Cytotoxic xanthone constituents of the stem bark of Garcinia mangostana (mangosteen). J Nat Prod 72, 2028–2031. https://doi.org/10.1021/np900517h

Handayani, S., Susidarti, R.A., Jenie, R.I., Meiyanto, E., 2017. Two Active Compounds from Caesalpinia sappan L. in Combination with Cisplatin Synergistically Induce Apoptosis and Cell Cycle Arrest on WiDr Cells. Adv Pharm Bull 7, 375–380. https://doi.org/10.15171/apb.2017.045

Hardhiyuna, M., Arbi, U.Y., Zuraida, Z., Ahmadi, P., 2024. Aaptamine-rich Fraction from the Indonesian Marine Sponge, Aaptos suberitoides, Exhibits a Cytotoxic Effect on DLD-1 Colorectal Cancer Cells. Asian Pac J Cancer Prev 25, 1737–1743. https://doi.org/10.31557/APJCP.2024.25.5.1737

Huang, M., Lu, J.-J., Ding, J., 2021. Natural products in cancer therapy: past, present and future. Biomedicine & Pharmacotherapy 133, 111103.

Illian, D.N., Hafiz, I., Meila, O., Utomo, A.R.H., Nuryawan, A., Siregar, G.A., Basyuni, M., 2021. Current Status, Distribution, and Future Directions of Natural Products against Colorectal Cancer in Indonesia: A Systematic Review. Molecules 26. https://doi.org/10.3390/molecules26164984

Illian, D.N., Hasibuan, P.A.Z., Sumardi, S., Nuryawan, A., Wati, R., Basyuni, M., 2019. Anticancer Activity of Polyisoprenoids from Avicennia alba Blume. in WiDr Cells. Iran J Pharm Res 18, 1477–1487. https://doi.org/10.22037/ijpr.2019.1100719

Jiso, A., Demuth, P., Bachowsky, M., Haas, M., Seiwert, N., Heylmann, D., Rasenberger, B., Christmann, M., Dietrich, L., Brunner, T., Riyanti, Schäberle, T.F., Plubrukarn, A., Fahrer, J., 2021. Natural Merosesquiterpenes Activate the DNA Damage Response via DNA Strand Break Formation and Trigger Apoptotic Cell Death in p53-Wild-type and Mutant Colorectal Cancer. Cancers (Basel) 13. https://doi.org/10.3390/cancers13133282

Kustiawan, P.M., Lirdprapamongkol, K., Palaga, T., Puthong, S., Phuwapraisirisan, P., Svasti, J., Chanchao, C., 2017. Molecular mechanism of cardol, isolated from Trigona incisa stingless bee propolis, induced apoptosis in the SW620 human colorectal cancer cell line. BMC Pharmacol Toxicol 18, 32. https://doi.org/10.1186/s40360-017-0139-4

Kustiawan, P.M., Phuwapraisirisan, P., Puthong, S., Palaga, T., Arung, E.T., Chanchao, C., 2015. Propolis from the Stingless Bee Trigona incisa from East Kalimantan, Indonesia, Induces In Vitro Cytotoxicity and Apoptosis in Cancer Cell lines. Asian Pac J Cancer Prev 16, 6581–6589. https://doi.org/10.7314/apjcp.2015.16.15.6581

Leong, K.H., Looi, C.Y., Loong, X.-M., Cheah, F.K., Supratman, U., Litaudon, M., Mustafa, M.R., Awang, K., 2016. Cycloart-24-ene-26-ol-3-one, a New Cycloartane Isolated from Leaves of Aglaia exima Triggers Tumour Necrosis Factor-Receptor 1-Mediated Caspase-Dependent Apoptosis in Colon Cancer Cell Line. PLoS One 11, e0152652. https://doi.org/10.1371/journal.pone.0152652

Li, R., Zheng, C., Shiu, P.H.-T., Rangsinth, P., Wang, W., Kwan, Y.-W., Wong, E.S.-W., Zhang, Y., Li, J., Leung, G.P.-H., 2023. Garcinone E triggers apoptosis and cell cycle arrest in human colorectal cancer cells by mediating a reactive oxygen species–dependent JNK

signaling pathway. Biomedicine & Pharmacotherapy 162, 114617. https://doi.org/10.1016/j.biopha.2023.114617

Ministry of Health of the Republic of Indonesia, 2022. Cancer Prevention and Control Framework.

Morgan, E. et al., 2023. Global burden of colorectal cancer in 2020 and 2040. Gut 72, 338–344.

Mutiah, R., Widyawaruyanti, A., Sukardiman, S., 2018. Calotroposid A: a Glycosides Terpenoids from Calotropis gigantea Induces Apoptosis of Colon Cancer WiDr Cells through Cell Cycle Arrest G2/M and Caspase 8 Expression. Asian Pac J Cancer Prev 19, 1457–1464. https://doi.org/10.22034/APJCP.2018.19.6.1457

Newman, D.J., Cragg, G.M., 2020. Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019. Journal of Natural Products 83, 770–803. https://doi.org/10.1021/acs.jnatprod.9b01285

Permatasanti, A., Hidayat, W., 2023. Potential of Indonesian herbal as an anti-cancer therapy. Cancer Management and Research 15, 837–850.

Purnomo, H.D. et al., 2023. Colorectal cancer screening in Semarang, Indonesia.

Rani, D.M. et al., 2023. Anti-cancer bioprospecting on medicinal plants from Indonesia. Phytochemistry.

Sari, D.P., Basyuni, M., Hasibuan, P.A., Sumardi, S., Nuryawan, A., Wati, R., 2018. Cytotoxic and Antiproliferative Activity of Polyisoprenoids in Seventeen Mangroves Species Against WiDr Colon Cancer Cells. Asian Pac J Cancer Prev 19, 3393–3400. https://doi.org/10.31557/APJCP.2018.19.12.3393

Sung, H., Ferlay, J., Siegel, R.L., Laversanne, M., Soerjomataram, I., Jemal, A., Bray, F., 2021. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians 71, 209–249. https://doi.org/10.3322/caac.21660

Tang, Y.L. et al., 2023. Resistance to targeted therapy in metastatic colorectal cancer.

Xi, Y., Xu, J., 2021. Global colorectal cancer burden in 2020 and projections to 2040.

Yao, Y. et al., 2021. Serious adverse events reporting in phase III trials of colorectal cancer treatments. Frontiers in Pharmacology 12, 754858.

Yoon, D., Choi, B.-R., Shin, W.C., Kim, K.-W., Lee, Y.-S., Lee, D.Y., 2023. Metabolomics reveals that Curcuma longa and demethoxycurcumin inhibit HCT116 human colon cancer cell growth. Appl Biol Chem 66, 84. https://doi.org/10.1186/s13765-023-00844-9

Yuliana, N.D., Tuarita, M.Z., Khatib, A., Laila, F., Sukarno, S., 2020. GC-MS metabolomics revealed protocatechuic acid as a cytotoxic and apoptosis-inducing compound from black rice brans. Food Sci Biotechnol 29, 825–835. https://doi.org/10.1007/s10068-019-00725-2