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Potential sources of chemopreventive agents from Indonesian plants against colorectal cancer: A review

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ABSTRACT

Colorectal cancer (CRC) is a serious health problem worldwide. The ever-increasing cases encouraged researchers to discover more effective novel drugs from plant sources. In this review, we summarized the plants contributing to the chemoprevention of CRC, as reported in *in vitro* animal studies and clinical trials. A literature search was conducted to collect information regarding the biological activities of plants from PubMed and Google Scholar, and also hand searching from other literature databases. 77 plants of 47 families cultivated in Indonesia were introduced as candidates for chemopreventive agents that help reduce cancer proliferation, progression, or recurrence. Phenolic compounds were revealed to have anticancer effects in most studies. *Allium sativum* L., *Zingiber officinale* Roscoe, *Annona muricata* L., and *Camellia sinensis* (L.) Kuntze, the fourth Indonesian plant only in a clinical trial, was able to reduce the risk of recurrence of colon adenoma, safe, and tolerated. Therefore, this review article could be key to conducting clinical trials on other plants to evaluate the safety and efficacy of developing new anticancer drugs against CRC.

INTRODUCTION

According to the WHO, 700,000 people die of colorectal cancer (CRC) yearly, which equals around 2,000 deaths daily (Sutrisna *et al*., 2018). With 34,783 cases (8.8% of all cancer cases in Indonesia), CRC is the fourth most common, following breast, cervical, and lung cancer. CRC is the second most frequent cancer in men, after lung cancer. In women, this cancer ranks fourth, following breast, cervical, and ovarian cancer. This suggests that CRC is more common in both men and women in Indonesia than in other cancers (Globocan, 2020a). Based on those data, CRC is the third most common cancer and the second leading cause of death worldwide (Globocan, 2020b).

Therapeutic approaches for human CRC include surgery, radiotherapy, chemotherapy, or a combination of those strategies (Nussbaumer *et al*., 2011). However, these approaches are unsatisfactory due to significant side effects (Hosseini and Ghorbani, 2015). Cancer treatment requires research for chemopreventive agents derived from plants that offer various degrees of protection against cancer with minimal adverse effects. Chemopreventive agent refers to using natural compounds, synthetics, or chemical/biological agents to reverse, inhibit, or prevent carcinogenesis (Tsao *et al*., 2000).

According to research, more than 50% of pharmaceutical drugs are derived from natural plant products (Chin *et al*., 2006). Indonesia has an abundance of flora that is utilized for food, welfare improvement, research, and traditional medicine. Traditional medicine comes from natural ingredients traditionally used for treatment based on experience. They assume that traditional or herbal medicines have fewer side effects than synthetic drugs (Haq *et al*., 1999).

There are numerous studies of traditional medicine as an alternative to chemotherapy for treating CRC due to its harmful side effects. However, its use is still limited, as health practitioners and physicians are still unwilling to prescribe it. This review aims to collect data on plants that have the potential as anticancer to be used as chemopreventive agents against CRC.

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METHODOLOGY

This study is using literature review that collects data and information from books, the internet, and well-published journals. The literature search was carried out in 2021. Then, the data was updated in July 2022. The literature search was conducted using search engines on PubMed and Google Scholar as well as hand searching from other literature databases. The keywords ("herbal" OR "extract" OR "medicinal plants") AND ("anticancer" OR "chemopreventive") AND ("CRC" OR "colon cancer") are used to search regarding Indonesian plants that potentially have anticancer effects against CRC. All the articles obtained met the eligibility criteria after screening by inclusion and exclusion criteria.

The inclusion criteria for articles from PubMed, Google Scholar, and hand searching are as follows:

1. Articles using extracts or fractions
2. Scopus indexed journals in English of Q1–Q3
3. SINTA-accredited national journal in Indonesian or English with a rank of S1–S3
4. Full text or free full text

The exclusion criteria used for articles from PubMed, Google Scholar, and hand searching are as follows:

1. Plants not cultivated in Indonesia
2. Using of isolates
3. Effects in a combination of two or several plants or cancer-related colon cancer drugs.

Articles obtained were classified based on preclinical studies and clinical trials. Figure 1 shows the flow chart of this study with the inclusion and exclusion criteria from databases.

RESULTS

Preclinical studies

The literature search found 96 articles related to preclinical studies of plants. Preclinical studies are classified into *in vivo* and *in vitro* research. The model and mechanism of crude drug treatment on colon tumorigenesis are presented in Table 1.

Clinical trial

There are six articles related to the clinical trial of plants. The type of studies, subjects, and also the outcome of formulation-

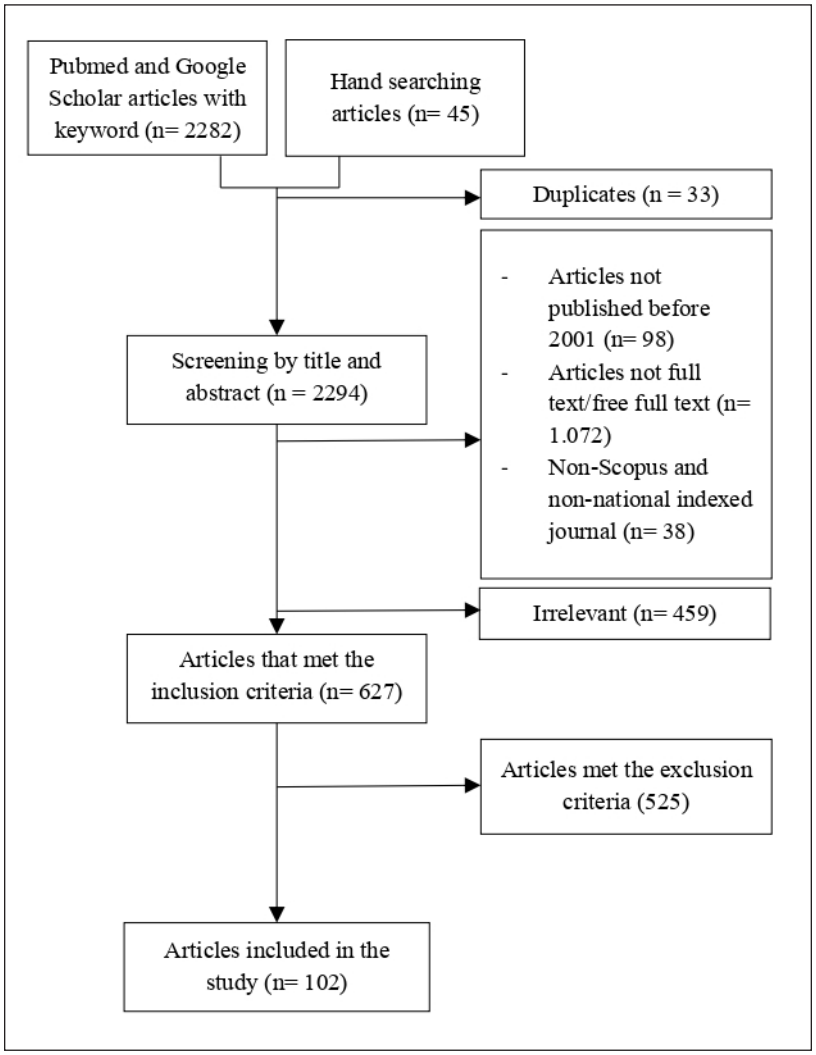

Figure 1. Flow chart of study selection process.

Table 1. Preclinical studies of effects of plants on colon tumorigenesis.

Plant name (Indonesian name)	Family	Extract(s) and part(s) used	Dose	Model(s)	Mechanisms	Signaling pathways		Experiment	Reference
						Decrease ↓	Increase ↑		
Acanthus ilicifolius L. (Jeruju)	Acanthaceae	Ethanol leaves extract	250 and 500 mg/kg	AOM-induced ACF of Sprague-Dawley rats	Reduce total colonic AOM-induced ACF formation and multicrypt aberrant crypt growth	Bcl-2	Bax p53	*In vivo*	(Almagrami *et al*., 2014)
Achyranthes aspera L. (Jarong)	Amaranthaceae	Ethanolic and aqueous root extract	50–200 µg/ml	COLO-205	Induction of apoptosis cells via the mitochondrial-mediated pathway; S cell-cycle arrest	Bcl-2	Caspase-9 Caspase-3 Bax p16 p21 p27	*In vitro*	(Arora and Tandon, 2015)
Allium fistulosum L. (Bawang daun)	Alliaceae	Aqueous herb extract	50 mg/kg	CT-26 cells inoculated into BALB/c mice (TXM)	Suppression of tumor growth	COX-2 INOS Cyclin D1 c-Myc VEGF HIF-1α MMP-9 ICAM-1	Apoptotic index	*In vivo*	(Arulselvan *et al*., 2012)
Allium sativum L. (Bawang putih)	Alliaceae	Hydroalcohol bulbus extract	0.1, 1, and 10 g/l	HT-29, SW480, and SW620	Inhibit proliferation cells; prevent tumor formation by inhibiting angiogenesis			*In vitro*	(Matsuura *et al*., 2006)
Aloe vera (L.) Burm. f. (Lidah buaya)	Asphodelaceae	Ekstrak methanol daun	10, 25, 50 µg dry weight/ml	HT-29	Inhibit proliferation and migration cells			*In vitro*	(Lima *et al*., 2020)
Alternanthera sessilis (L.) R.Br. ex DC. (Kremah)	Amaranthaceae	Ekstrak etanol herba, batang, dan daun	25–500 µg/ml	HT-29	Suppressed the growth of cells			*In vitro*	(Gothai *et al*., 2018)
Amaranthus gangeticus L. (Bayam merah)	Amaranthaceae	Aqueous and ethanol leaves extract	5–100 µg/ml	Caco-2	Inhibit viability of cells			*In vitro*	(Sani *et al*., 2004)
Amorphophallus campanulatus (Roxb.) Blume (Suweg)	Araceae	Methanolic tuber extract, petroleum ether; chloroform; ethyl acetate; methanolic tuber fraction	50 and 100 µg/ml	HCT-115	Inhibit proliferation and induce apoptosis cell death			*In vitro*	(Ansil *et al*., 2014)

Plant name (Indonesian name)	Family	Extract(s) and part(s) used	Dose	Model(s)	Mechanisms	Signaling pathways		Experiment	Reference
						Decrease ↓	Increase ↑		
		Methanol tuber extract	250 and 500 mg/kg	DMH-induced ACF of Sprague-Dawley rat	Suppress the formation and multiplicity of ACF	PCNA		*In vivo*	(Ansil *et al.*, 2013)
Andrographis paniculata (Burm. f.) Nees (Sambiloto)	Acanthaceae	Ethanol herb extract	250 and 500 mg/kg	AOM-induced ACF of Sprague-Dawley rats	Antioxidant activity; reduction number of ACF	PCNA β-catenin		*In vivo*	(Al-Henhena *et al.*, 2014)
Annona muricata L. (Sirsak)	Annonaceae	Ethanol leaves extract	15.625–400 µg/ml	COLO-205	Enhancing proapoptotic marker; inducing apoptosis of cells		Caspase-3	*In vitro*	(Abdullah *et al.*, 2017)
		Ethanol seed extract	5–300 µg/ml	WiDr	Inhibit the proliferation of cells			*In vitro*	(Arifianti *et al.*, 2014)
		Ethyl acetate leaves extract	10–80 µg/ml	HT-29 and HCT-116	Inhibiting the proliferation of cells; G1 cell-cycle arrest; induction of apoptosis; blocking the migration and invasion of cells	Bcl-2	Bax	*In vitro*	(Moghadamtousi *et al.*, 2014)
		Ethyl acetate leaves extract	250 and 500 mg/kg	AOM-induced ACF of rats	Inhibit the growth of ACF colony	PCNA Bcl-2	Bax	*In vivo*	(Moghadamtousi *et al.*, 2015)
Annona squamosa L. (Srikaya)	Annonaceae	Methanol, acetone, and aqueous leaves fraction	100 µg/ml	LoVo and HCT-116	Antioxidant activity; inhibiting the growth and migration of cells; inducing apoptosis cell death			*In vitro*	(Al-Nemari *et al.*, 2020)
Arcangelisia flava (L.) Merr. (Akar kuning)	Menispermaceae	Ethanol stems extract	31.25–500 µg/ml	WiDr	Inhibit cells growth			*In vitro*	(Mutiah *et al.*, 2020b)
Artemisia vulgaris L. (Baru cina)	Asteraceae	Methanol herb extract	10–200 µg/ml	HCT-115	Inhibiting proliferation; colony formation and migration; induction autophagy of cells			*In vitro*	(Lian *et al.*, 2018)

Plant name (Indonesian name)	Family	Extract(s) and part(s) used	Dose	Model(s)	Mechanisms	Signaling pathways		Experiment	Reference
						Decrease ↓	Increase ↑		
Azadirachta indica A. Juss. (Mimba)	Meliaceae	Ethanolic and aqueous leaves extract	0.06–1 mg/ml	HT-29	Induce apoptosis of cells			*In vitro*	(Roma *et al.*, 2015)
		Aqueous leaves extract	20–250 mg/kg	AOM-induced ACF of Sprague-Dawley rats	Inhibit the induction of ACF	PCNA		*In vivo*	
Brassica juncea (L.) Czern. (Sawi)	Cruciferae	Ethanolic leaves extract	175–700 µg/ml	HCT-116	Inhibiting cell growth; induction apoptosis; suppressing the secretion of pro-angiogenic factor; inhibiting invasion, migration, and adhesion of cells			*In vitro*	(Kwak *et al.*, 2016)
Brucea javanica (L.) Merr. (Buah makassar)	Simaroubaceae	Ethanol fruit extract	25–100 µg/ml	HT-29	Induce cell apoptosis via mitochondrial-dependent and -independent event	Bcl-2	Cytochrome-c Bax Bad Caspase-9	*In vitro*	(Bagheri *et al.*, 2018)
Caesalpinia sappan L. (Secang)	Caesalpiniaceae	Ethanol heartwood extract	2.5–30 µg/ml	WiDr	Inhibit viability of cells			*In vitro*	(Rivanti *et al.*, 2017)
Cajanus cajan (L.) Millsp. (Gude)	Leguminosae	Methanol leaves extract	100–500 µg/ml	WiDr	Inhibiting the proliferation of cells; induction apoptosis			*In vitro*	(Rahayu and Roosmarinto, 2017)
Camellia sinensis (L.) Kuntze (Teh putih)	Theaceae	White tea aqueous leaves extract	10–100 µg/ml	HT-29	Antioxidant activity; inhibiting proliferation of cells		Caspase-3 Caspase-8 Caspase-9	*In vitro*	(Hajiaghaalipour *et al.*, 2015)
		Green tea hydroalcoholic leaves extract	50–800 µg/ml	Caco-2	Inhibit of growth of cells	Aquaporin 5		*In vitro*	(Esghaei *et al.*, 2018)
Carthamus tinctorius L. (Kesumba)	Asteraceae	Ethanol seeds extract	100 µg/ml	RKO	Inhibit viability of cells			*In vitro*	(Park *et al.*, 2019)
		Ethanol seed extract	100 and 200 mg/kg	RKO cells inoculated into BALB/c mice (TXM)	Inhibit proliferation and decrease the weight of cells			*In vitro*	

Plant name (Indonesian name)	Family	Extract(s) and part(s) used	Dose	Model(s)	Mechanisms	Signaling pathways		Experiment	Reference
						Decrease ↓	Increase ↑		
Chromolaena odorata (L.) R.M.King & H.Rob. (Kirinyu)	Asteraceae	Hexane leaves extract	62.5–1,000 µg/ml	WiDr	Antioxidant activity; inhibiting viability of cells			*In vitro*	(Leboe *et al.*, 2005)
Cinnamomum cassia (L.) J.Presl (Kayu manis)	Lauraceae	Aqueous twigs extract	50–200 µg/ml	HCT116, SW480, LoVo, and HT-29	Suppress cell proliferation; induce apoptosis	Cyclin D1		*In vitro*	(Park *et al.*, 2018)
Citrus reticulata Blanco (Jeruk keprok)	Rutaceae	Ethanol peel extract	10–240 µg/ml	WiDr	Inhibit viability; inhibit migration of cells			*In vitro*	(Astuti and Primasari, 2020)
Coix lacryma-jobi L. (Jali)	Poaceae	Aqueous herb extract	0.25–10 mg/ml	HCT-116	Blocking cells migration; reducing invasive cells; inhibiting adhesion of cells	Deferoxamine		*In vitro*	(Son *et al.*, 2017)
Coleus amboinicus Lour. (Torbangun)	Lamiaceae	Methanol leaves extract	1–100 µg/ml	WiDr	Inhibiting proliferation of cells; induction apoptosis cell death	Bcl-2	Bax p53 Caspase-9	*In vitro*	(Laila *et al.*, 2020)
Cucurbita pepo L. (Zukini)	Cucurbitaceae	Ethanol seed extract	100–200 mg/kg	DMH-induced ACF of Wistar rats	Decrease hyperplasia and ACF			*In vivo*	(Chari *et al.*, 2018)
Curcuma mangga Valeton & Zijp (Temu mangga)	Zingiberaceae	Ethyl acetate and hexane rhizomes extract	1–100 mg/ml	HT-29	Inhibiting viability of cells; G_0/G cell-cycle arrest; induction apoptosis			*In vitro*	(Hong *et al.*, 2016)
Curcuma purpurascens Blume (Temu tis)	Zingiberaceae	Dichloromethane rhizomes extract	12.5 and 25 µg/ml	HT-29	Inducing proliferation of cells; induction apoptosis via mitochondrial-dependent pathway	Bcl-2	Bax	*In vitro*	(Rouhollahi *et al.*, 2015a)
		Dichloromethane rhizome extract	250 and 500 mg/kg	AOM-induced ACF of Sprague-Dawley rats	Decrease ACF formation	PCNA Bcl-2	Bax	*In vivo*	(Rouhollahi *et al.*, 2015b)
Cymbopogon citratus (DC.) Stapf (Serai)	Poaceae	Ethanol herb extract	0.01 and 0.025 µg/ml	HT-29 and HCT-116	Induced apoptosis cell death			*In vitro*	(Ruvinov *et al.*, 2019)

Plant name (Indonesian name)	Family	Extract(s) and part(s) used	Dose	Model(s)	Mechanisms	Signaling pathways		Experiment	Reference
						Decrease ↓	Increase ↑		
		Ethanol herb extract	16 mg/kg	HCT-116 and HT-29 cells inoculated into BALB/c mice (TXM)	Inhibit colon cancer xenograft growth			*In vivo*	
Dendrophthoe pentandra (L.) Miq (Kemladean)	Loranthaceae	Ekstrak etanol daun	125, 250, and 500 mg/kg	AOM- and DSS-induced ACF of Balb/c mice	Preventing proliferation of cells; inhibition of S phase	MPO IL-22	p53	*In vivo*	(Endharti *et al.*, 2016)
Diospyros kaki L.f. (Kesemek)	Verbenaceae	Ethanol calyx extract	25–100 µg/ml	HCT-116	Suppressed the proliferation of cells	Cyclin D1 β-catenin TCF4		*In vitro*	(Park *et al.*, 2017)
Eclipta alba (L.) Hassk. (Urang-aring)	Asteraceae	Methanol herb extract	50–500 µg/ml	HCT-116	Inhibit proliferation of cells; inhibit migration and colony formation of cells			*In vitro*	(Nelson *et al.*, 2020)
Eleutherine palmifolia (L.) Merr. (Bawang dayak)	Iridaceae	Ekstrak etanol umbi	0.25, 0.5, and 1 mg/20g	AOM- and DSS-induced CAC of Balb/c mice	Increase the goblet cell in reducing the severity of colitis; induce apoptosis	TGF-β	TNF-α	*In vivo*	(Mutiah *et al.*, 2020a, 2020c)
Eugenia jambolana Lam. (Jamblang)	Myrtaceae	Aqueous fruit extract	30 and 40 µg/ml	HCT-116	Suppress growth of cells; inhibit colony formation			*In vitro*	(Charepalli *et al.*, 2016)
Euphorbia helioscopia L. (Patikan Kebo)	Euphorbiaceae	Ethyl acetate herb extract	100–200 µg/ml	SW-480	Inhibit viability of cells			*In vitro*	(Wang *et al.*, 2012)
Flacourtia indica (Burm. f.) Merr. (Bonsai rukem)	Salicaceae	Methanol herb extract	500 µg/ml	HCT-116	Reduce cell viability; induce apoptosis	Bcl-2 Bcl-xl Survivin	Cytochrome c Caspase-3	*In vitro*	(Park *et al.*, 2014a)
Garcinia mangostana Linn. (Manggis)	Clusiaceae	Ethanol pericarp extract	10–30 µg/ml	WiDr	Reduce cell viability; induce apoptosis			*In vitro*	(Rohmah *et al.*, 2013)
Glycine max (L.) Merr. (Kedelai)	Fabaceae	Ethanol leaves extract	125, 250, and 500 µg/ml	HCT-116	Inhibit proliferation of cells; inhibit colony formation, migration, and adhesion of cells	NO PGE2		*In vitro*	(Kwak and Ju, 2017)

Plant name (Indonesian name)	Family	Extract(s) and part(s) used	Dose	Model(s)	Mechanisms	Signaling pathways		Experiment	Reference
						Decrease ↓	Increase ↑		
Glycyrrhiza glabra L. (Akar manis)	Fabaceae	Ethanol root extract	200 µg/ml	HT-29	Inhibiting proliferation of cells; induction of apoptosis cells	HSP90		*In vitro*	(Nourazarian *et al.*, 2016)
Gnetum gnemon L. (Melinjo)	Gnetaceae	Ethanol seed extract	1.25–400 µg/ml	HT-29	Inhibit proliferation of cells; induce apoptosis death cells			*In vitro*	(Narayanan *et al.*, 2015)
		Ethanol seed extract	50 and 100 mg/kg	Colon-26 cells inoculated into BALB/c mice (TXM)	Inhibit tumor cell growth, intratumoral angiogenesis, and liver metastasis; induce apoptosis of cells			*In vivo*	
Graptophyllum pictum (L.) Griff (Daun wungu)	Acanthaceae	n-Hexane leaves fraction	5–2,000 µg/ml	WiDr	Inhibit proliferation of cells			*In vitro*	(Amin *et al.*, 2020)
Guazuma ulmifolia L. (Jati belanda)	Malvaceae	Ethanol leaves extract	12.5–500 µg/ml	WiDr	Inhibit proliferation of cells			*In vitro*	(Da'i, 2015)
Gynura procumbens (Lour.) Merr. (Sambung nyawa)	Asteraceae	Ethyl acetate leaves fraction	50–1,000 µg/ml	WiDr	Inhibit proliferation of cells			*In vitro*	(Nurulita *et al.*, 2011)
		Ethanol leaves extract	250 and 500 mg/kg	AOM-induced ACF of Sprague-Dawley rats	Reduce the total crypts	Bcl-2		*In vivo*	(Shwter *et al.*, 2014)
Hedyotis corymbosa L. (Rumput mutiara)	Rubiaceae	Ethanol herb extract	10–125 µg/ml	WiDr	Inhibit proliferation of cells; G_1/S cell-cycle arrest	Cyclin D		*In vitro*	(Meiftasari *et al.*, 2016)
Hedyotis diffusa Willd. (Rumput lidah ular)	Rubiaceae	Ethanol herb extract	0.5, 1, and 2 mg/ml	HCT-8, HT-29, HCT-116, and SW620	Inhibit growth of cells and angiogenesis; promote apoptosis	Pim-1 Bcl-2 COX-2 iNOS eNOS HIF-1α	Bax PARP Caspase-3 Caspase-9		(Feng *et al.*, 2017)

Plant name (Indonesian name)	Family	Extract(s) and part(s) used	Dose	Model(s)	Mechanisms	Signaling pathways		Experiment	Reference
						Decrease ↓	Increase ↑		
		Ethanol herb extract	0.5–5 mg/ml	HT-29	Inhibiting viability of cells; inhibiting colony formation; induction of apoptosis; inhibiting angiogenesis	Bcl-2	Bax	*In vitro*	(Lin *et al*., 2009, 2013)
		Chloroform herb extract	50, 75, 100 µg/ml	SW620	Suppress proliferation; promote apoptosis of cells	Survivin PCNA Cyclin D1 Cyclin-dependent kinase 4		*In vitro*	(Yan *et al*., 2017)
		Aqueous herb extract	25–200 µg/ml	HCT-116, DLD-1, HT-29, and LoVo	Inhibit proliferation of cells; induce apoptosis of cells	Bcl-2		*In vitro*	(Lu *et al*., 2016)
Hedyotis diffusa Willd. (Rumput lidah ular)	Rubiaceae	Ethanol herb extract	1 g/kg	HT-29 cells inoculated into BALB/c mice (TXM)	Inhibit the growth of tumor; promote apoptosis; inhibit sonic Hedgehog and antiangiogenesis <AQ>	Pim-1 Bcl-2 COX-2 iNOS eNOS HIF-1α VEGF-A VEGFR2	Cytochrome c Caspase-9 PARP Bax	*In vivo*	(Feng *et al*., 2017; Lin *et al*., 2013)
Hibiscus cannabinus L. (Kenaf)	Malvaceae	Ethanol seed extract	15.625–10,000 µg/ml	HCT-116	Inhibit proliferation of cells; induce apoptosis of cells			*In vitro*	(Wong *et al*., 2014)
Houttuynia cordata Thunb. (Amis-amisan)	Saururaceae	Ethanol herb extract	450 µg/ml; 125, 250, and 500 µg/ml	HT-29 and human primary CRC	Inhibit viability of cells; induce apoptosis of cells	Bcl-2	Cytochrome c Apaf-1 Caspase-9 Bax		(Lai *et al*., 2010; Tang *et al*., 2010)
Litchi chinensis Sonn. (Leci)	Sapindaceae	Ethanol seed extract	12.5–150 µg/ml	Colo320DM and SW480	Inhibiting growth of cells; inducing apoptosis of cell growth; G_2/M cell-cycle arrest	Bcl-2	Cyclins Bax Caspase-3	*In vitro*	(Hsu *et al*., 2012)

Plant name (Indonesian name)	Family	Extract(s) and part(s) used	Dose	Model(s)	Mechanisms	Signaling pathways		Experiment	Reference
						Decrease ↓	Increase ↑		
Mangifera indica L. (Mangga)	Anacardiaceae	Ethanol peel extract	180–600 µg/ml	HT-29, CaCo-2, and HCT-116	Inhibit viability of cells; promote apoptosis		Nrf2 MnSOD	*In vitro*	(Lauricella *et al.*, 2019)
Melissa officinalis L. (Lemon balm)	Lamiaceae	Aqueous leaves extract	250, 375, and 500 µg/ml	HCT-116	Inhibit viability of cells; G_2/M cell-cycle arrest; inhibit migration; promote apoptosis	N-cadherin	E-Cadherin Caspase 3/7	*In vitro*	(Kuo *et al.*, 2020)
		Hydroalcoholic leaves extract	0.5–1,000 µg/ml	HT-29 and T84	Inhibiting proliferation of cells; G_2/M cell-cycle arrest	CDK 2,4,6 Cyclin D3	p18 p21 Caspase-3 Caspase-7	*In vitro*	(Weidner *et al.*, 2015)
Mentha arvensis L. (Bijanggut)	Lamiaceae	Aqueous and methanol herb extract	200 µg/ml	COLO-205 and HCT-116	Inhibit proliferation of cells			*In vitro*	(Sharma *et al.*, 2014)
Momordica charantia L. (Pare)	Cucurbitaceae	Methanol leaves extract	0.2 and 0.35 mg/ml	HCT-116	Inhibit viability of cells; induce apoptosis via mitochondrial pathway	Bcl-2	Caspase-3 Bax	*In vitro*	(Li *et al.*, 2012)
Moringa oleifera Lam. (Kelor)	Moringaceae	Ethanol bark and leaves extract	250 and 500 µg/ml <AQ>	HCT-8	Inhibiting proliferation of cells; inhibiting motility and colony formation; G_2/M cell-cycle arrest			*In vitro*	(Al-Asmari *et al.*, 2015)
		Aqueous seed extract	6%	AOM-induced ACF of Sprague-Dawley rats	Decrease incidences and multiplicities of tumor	PCNA iNOS COX-2		*In vivo*	(Budda *et al.*, 2011)
Morus alba L. (Bebesaran)	Moraceae	Ethanol stem extract	7.8–1,000 µg/ml	WiDr	Inhibit viability of cells			*In vitro*	(Burhan *et al.*, 2020)
Muntingia calabura L. (Kersen)	Muntingiaceae	Methanol leaves extract	500 mg/kg	AOM-induced ACF of Sprague-Dawley rats	Inhibit proliferation of ACF			*In vivo*	(Nasir *et al.*, 2017)
Origanum majorana L. (Marjoram)	Lamiaceae	Ethanol leaves extract	150–600 µg/ml	HT-29 and Caco-2	Inhibit proliferation of cells; inhibit colony growth; induce mitotic arrest and apoptosis	Survivin	Caspase-3 Caspase-7	*In vitro*	(Benhalilou *et al.*, 2019)
Orthosiphon Stamineus Benth. (Kumis kucing)	Lamiaceae	Ethanol leaves extract	3.625–100 µg/ml	HCT-116	Suppress angiogenesis of cells			*In vitro*	(Ahamed *et al.*, 2012)

Plant name (Indonesian name)	Family	Extract(s) and part(s) used	Dose	Model(s)	Mechanisms	Signaling pathways		Experiment	Reference
						Decrease ↓	Increase ↑		
		Ethanol leaves extract	100 and 200 mg/kg	HCT-116 cells inoculated into BALB/c mice (TXM)	Suppressing tumor growth; antiangiogenicity			*In vivo*	
Phaleria macrocarpa (Scheff.) Boerl. (Mahkota dewa)	Thymelaeaceae	Ethanol leaves extract	25 and 50 mg/kg	AOM- and DSS-induced CAC of Balb/c mice	Inhibit proliferation of tumor; prevent decreasing the goblet cells			*In vivo*	(Rakasiwi *et al*., 2020)
Phyllanthus reticulatus Poir. (Mangisan)	Phyllanthaceae	Aqueous and ethanol herb extract	7.8–1,000 µg/ml	HT-29	Inhibit proliferation of cells			*In vitro*	(Aarthi and Babu, 2017)
Physalis angulata L. (Ceplukan)	Solanaceae	Ethanol herb extract	7.81–1,000 µg/ml	WiDr	Inhibit viability of cells			*In vitro*	(Djajanegara, 2008)
Piper betle L. (Sirih hijau)	Piperaceae	Aqueous leaf extract	100–1,200 µg/ml	HCT-116 and HT29	Inhibiting proliferation of cells; S and G_2/M cell-cycle arrest; inducing apoptosis	Bcl-2 TP53	Caspase-3 Caspase-8	*In vitro*	(Yusof *et al*., 2022)
Piper crocatum Ruiz & Pav. (Sirih merah)	Piperaceae	Methanol leaves extract	10–150 µg/ml	WiDr	Inhibit viability of cells; promote apoptosis			*In vitro*	(Wulandari *et al*., 2018)
Piper longum L. (Lada panjang)	Piperaceae	Ethanol fruit extract	0.1, 0.2, and 0.4 mg/ml	HCT-116	Induce caspase-independent apoptosis			*In vitro*	(Ovadje *et al*., 2014)
		Ethanol fruit extract	50 mg/kg	HT-29 and HCT-116 cells inoculated into CD-1 nu/nu mice (TXM)	Halt the growth of tumor			*In vivo*	
Pogostemon cablin Benth. (Nilam)	Lamiaceae	Aqueous leaves extract	5.83–93.2 µg/ml	HT-29	Inhibiting viability of cells; G_0/G_1 cell-cycle arrest	CDK4 Cyclin D1 MMP2/MMP9	p53 p21	*In vitro*	(Chien *et al*., 2020)
		Aqueous leaves extract	200 mg/kg	CT-26 cells inoculated into BALB/c mice (TXM)	Inhibit the growth of cells; induce apoptosis			*In vivo*	
Portulaca oleracea L. (krokot)	Portulacaceae	Ethyl alcohol extract	0.07–2.25 µg/ml	HT-29	Inhibit proliferation of cells; promote apoptosis	Notch1 β-catenin		*In vitro*	Jin *et al*. (2017)
Solanum Nigrum L. (Leunca)	Solanaceae	Ethanol herb extract	50–500 µg/ml	WiDr	Inhibit viability of cells			*In vitro*	(Maruti *et al*., 2011)

Plant name (Indonesian name)	Family	Extract(s) and part(s) used	Dose	Model(s)	Mechanisms	Signaling pathways		Experiment	Reference
						Decrease ↓	Increase ↑		
Strobilanthes crispa (L.) Blume (Keji beling)	Acanthaceae	Ethanol leaves extract	250 and 500 mg/kg	AOM-induced ACF of Sprague-Dawley rats	Reduce the number of ACF	PCNA Bcl-2 β-catenin		*In vitro*	(Al-Henhena *et al.*, 2015a)
		Methanol and ethyl acetate leaves fraction	100–500 µg/ml	HT-29	Inhibit proliferation of cells; decrease colon			*In vitro*	(Al-Henhena *et al.*, 2015b)
Taraxacum officinale (L.) Weber ex F. H. Wigg. (Randa tapak)	Asteraceae	Aqueous root extract	0.5–4 mg/ml	HCT-116 and HT-29	Promote apoptosis of cells; inhibit proliferation and migration of cells			*In vitro*	(Ovadje *et al.*, 2016)
		Ekstrak air akar	40 mg/kg	HCT-116 and HT-29 cells inoculated into BALB/c mice (TXM)	Suppress the growth of both cells			*In vivo*	
Tinospora cordifolia (Willd.) Miers (Brotowali)	Menispermaceae	Methanol-water	92–309 µg/ml	HCA-7	Suppress growth of cells			*In vitro*	(Palmieri *et al.*, 2019)
Typhonium flagelliforme (Lodd.) Blume (Keladi tikus)	Araceae	Ethyl acetate leaves extract	3.16–1,000 µg/ml	WiDr	Inhibiting viability of cells; promoting apoptosis; inhibition of COX-2 expression			*In vitro*	(Setiawati *et al.*, 2016)
Urtica dioica L. (Jelatang)	Urticaceae	Dichloromethane herb extract	10–60 µg/ml	HCT-116	Inhibiting proliferation of cells; inducing apoptosis; G_2 cell-cycle arrest	Bcl-2	Caspase-3 Caspase-9	*In vitro*	(Mohammadi *et al.*, 2016)
		Diethyl ether seed extract	30 ml/kg	AOM-induced colon carcinogenesis of Wistar rats	Decrease aberrant crypt foci, adenoma, and adenocarcinoma formation	CEA COX-2	Caspase-3	*In vivo*	(Uyar *et al.*, 2021)
Voacanga foetida (Blume) Rolfe (Tampa badak)	Apocynaceae	Ethyl acetate leaves extract	0.1, 0.5, and 1 µg/ml	HTB-38	Inhibit viability of cells			*In vitro*	(Susanty *et al.*, 2018)
Zanthoxylum armatum DC. (Andaliman)	Rutaceae	Methanol leaves, bark, and fruit extract	200–500 µg/ml	Caco-2	Inhibit growth of cells; induce apoptosis of cell death			*In vitro*	(Alam *et al.*, 2017)
Zingiber officinale Roscoe (Jahe)	Zingiberaceae	Aqueous rhizome extract	2–10 mg/ml	HCT-116	Inhibit viability of cells			*In vitro*	(Hakim *et al.*, 2014)
		Ethyl acetate leaves fraction	50, 100, and 200 µg/ml	HCT116, SW480, and LoVo	Inhibit viability of cells; promote apoptosis		ATF3	*In vitro*	(Park *et al.*, 2014b)

Plant name (Indonesian name)	Family	Extract(s) and part(s) used	Dose	Model(s)	Mechanisms	Signaling pathways		Experiment	Reference
						Decrease ↓	Increase ↑		
		Ethanol rhizome extract	300–1,500 µg/ml	HCT116 and HT29	Inhibiting proliferation of cells; S and G2/M cell-cycle arrest; promoting apoptosis of cell death	Bcl-2	TP53 Caspase-3 Caspase-8	*In vitro*	(Yusof *et al.*, 2022)
Ziziphus spina-christi (L.) Desf. (Bidara arab)	Rhamnaceae	Aqueous fruit extract		AOM-induced ACF of Sprague-Dawley rats	Reduce aberrant crypt foci development		Caspase-3	*In vivo*	(Guizani *et al.*, 2013)

AOM = Azoxymethane; ACF = Aberrant crypt foci; TXM = Tumor xenograft model; DMH = 1,2- Dimethylhydrazine; PCNA = Proliferation cell nuclear antigen; DSS = Dextran sodium sulfate; CAC = Colitis-associated colon cancer; CEA = Carcinoembryonic antigen; MPO = Myeloperoxidase.

contained crude drug treatment on colon tumorigenesis are presented in Table 2.

DISCUSSION

Lamiaceae is the most dominant compared to other families. According to a study, Lamiaceae is the largest family of flowering plants, consisting of 250 genera, and more than 7,000 species. Essential oils from the Lamiaceae family have been evaluated for their anticancer properties and can be exploited as a source for anticancer medicines. The underlying mechanisms are antiproliferative action, induction of cell cycle arrest, apoptosis, and DNA repair (Mesquita *et al*., 2019; Venkateshappa and Sreenath, 2013). Several classes of chemicals, including glycosides, flavonoids, and phenols, are abundant in numerous Lamiaceae that are rich in terpenoids (Özgen *et al*., 2006). Terpenoids are able to inhibit nuclear factor- κB (NF- κB), a key regulator in the pathogenesis of inflammation and cancer (Salminen *et al*., 2008).

In this study, each plant has a variety of groups of compounds that exhibit anticancer effects on CRC. This study revealed that the medicinal plants in Indonesia contain compounds targeting cancer cells that inhibit the growth and destruction of tumor cells. Most studies showed that phenolic compounds exhibit anticancer effects on various types of colon cells. Phenol compounds are able to scavenge peroxide radicals and chelate the ferrous metals that catalyze lipid peroxides (Pavarini *et al*., 2012). In addition, phenolic compounds exhibit anticancer effects on cell proliferation processes such as cell cycle arrest, apoptosis, angiogenesis, inhibition of topoisomerase II, and the impact on the pathways of phosphoinositide 3-kinase (PI3-K) and protein kinase B (Akt) (Asadi-Samani *et al*., 2016).

Moreover, Wang *et al*. (2012) found that only the ethyl acetate extract of *Euphorbia helioscopia* L. (patikan kebo) reduced the viability of SW-480 cancer cells, but the petroleum ether, chloroform, and butanol extracts had no effect. The active substances of *E. helioscopia* L. (patikan kebo) are primarily flavonoids and diterpenoids. *In vitro* assay, flavonoids induce apoptosis by cell cycle arrest and prevent migration and proliferation of cancer cells (Wang *et al*., 2012).

D-Allose, a compound of Moringa leaf (*Moringa oleifera* L.), inhibits the proliferation of cancer cells in the G1 phase by stimulation of specific thioredoxin interacting protein and stabilization of p27kip1 protein without affecting normal cells. Isothiocyanates (organosulfur compounds) present in the stem skin of Moringa (*M. oleifera* L.) have anticancer properties (Al-Asmari *et al*., 2015). However, in most studies, several compounds of the plants have not been reported as exactly being responsible for anticancer effects, which should be further investigated.

Various anticancer agents that have shown efficacy *in vitro* have failed to exhibit the same efficacy *in vivo* due to poor stability and bioavailability (Ruvinov *et al*., 2019). The xenograft model of a tumor plays an important role in testing novel anticancer drugs. This cancer model is developed by injecting human cancer-derived cells into the animal (Jung, 2014). Azoxymethane (AOM) (C2H6N2O), a metabolite of 1,2-Dimethylhydrazine (DMH), is a carcinogen used to promote colonic neoplasia in rodents. DMH is metabolized in the liver to form reactive and carcinogenic methyl diazonium ions via the intermediates AOM and methylazoxymethanol. When methyl diazonium ions are formed,

Table 2. Human studies of plants and colon tumorigenesis.

Plant name	Family name	Subject	Type of study	Formulation/Dose	No. of subjects	Length of study	Outscome	Reference
Allium sativum L. (Bawang putih)	Alliaceae	Carrying colorectal adenomas and polypectomy patients	Randomized controlled trial	High dose (2.4 ml/ day) and low dose (0.16 ml/day) of capsule containing extract; 6 capsules/ day	51	12 months	Suppress size, number, and progression of colon adenoma of high-dose treatment	(Tanaka *et al*., 2006)
Annona muricata L. (Sirsak)	Annonaceae	Polypectomy patients	*Ex vivo* and Randomized controlled trial	Ethanol-soluble fraction of water extract (0.36 mg/g acetogenin)/ 300 mg/day	28	8 weeks	Inhibit and decrease viability of cells	(Indrawati *et al*., 2017a, 2017b)
Camellia sinensis (L.) Kuntze (Teh hijau)	Theaceae	Polypectomy patients	Pilot study	Tablet containing green tea extract (equivalent to 2 Japanese-size cups of green tea)/3 tablets/day	125	12 months	Prevent incidence of metachronous adenomas	(Hu *et al*., 2016; Shimizu *et al*., 2008)
Zingiber officinale Roscoe (Jahe)	Zingiberaceae	Healthy patients	Randomized controlled trial	Capsule containing ginger rhizome extract (250 mg/ capsule)/2 g/day	30	28 days	Decrease eicosanoid levels by inhibiting synthesis from arachidonic acid	(Zick *et al*., 2011)

carbonium ions are produced, which are known to induce oxidative stress, DNA alkylation, DNA damage, and mutations (Perše and Cerar, 2010). In addition to AOM, dextran sulfate sodium (DSS) or a combination of those may also be utilized. In an experimental model of human-like colon cancer, AOM and DSS were developed. The formation of colon cancer by these carcinogens begins with the pathogenesis of epithelial cells into small lesions such as abnormal crypt foci (ACF). ACF is considered a precancerous condition in both animal and human colorectal models. This model has been utilized as an intermediate biomarker to rapidly assess the CRC prevention potential of chemopreventive drugs (Uyar *et al*., 2021).

In this study, 16 plants were *in vitro* and *in vivo* exhibited in-line effects. Park *et al*. (2019) investigated the ethanol extract of *Carthamus tinctorius* L. (kesumba) seeds against RKO colon cancer cells and RKO colon cancer cell-implanted xenograft mice-bearing tumors. In both *in vitro* and *in vivo* experiments, the ethanol extract of *C. tinctorius* L. (kesumba) seeds reduced the viability of RKO cancer cells, inhibited growth, and decreased tumor weight.

Oxidative stress is a condition that may cause harm to physiological and biochemical processes. Overproduction of free radicals may also cause oxidative damage to biomolecules such as DNA, proteins, and lipids. This process may eventually lead to numerous chronic diseases like cancer (Baradaran *et al*., 2014; Madihi *et al*., 2013).

Carcinogens can also generate free radicals in colonic tissue, which can be neutralized by antioxidants that consist of enzymatic antioxidants such as catalase (CAT), glutathione peroxidase (GPx), and glutathione reductase (GR) as well as non-enzymatic antioxidants as tripeptide glutathione (GSH), which are the primary defense system against free radicals in the biological system. CAT and GPx were proposed as the principal antioxidant enzymes because they eliminate reactive oxygen species (ROS). Low CAT activity in cancerous tissue will facilitate cancer growth and infiltration into adjacent tissues. Glutathione-S-transferase and GR are secondary antioxidant enzymes that aid in ROS detoxification by decreasing peroxide levels or preserving metabolic intermediates such as GSH. GSH and other enzymes collaborate to shield cells against ROS (Sreedharan *et al*., 2009).

Most medicinal plants with anticancer properties contain phenolic compounds with antioxidant activity. They can also decrease the toxicity of substances that generate oxidative stress. The presence of hydroxyl groups in phenolic substances is responsible for their antioxidant properties. These plants may therefore exert their anticancer effects by scavenging free radicals (Lam *et al*., 2007; Pahari *et al*., 2012).

There are several mechanisms based on the presence of compounds in plants, both cellular and molecular. Based on the data, cellular mechanisms include inhibiting cancer cell proliferation or decreasing cancer cell viability and inhibiting colonization, cancer cell migration, and invasion. The molecular mechanisms are such as induced apoptosis by inducing cell cycle arrest at G0/G1, G1, G2, S, G1/S, or G2/M phases; decreased expression of antiapoptotic (Bcl-2 and Bcl-xL) and proapoptotic proteins (Bad, Bax), cyclin D, cyclin-dependent kinase 4, cyclin-dependent kinase inhibitor 2C (p18) or 1A (p21), and survivin; increased expression of cell cycle inhibitors, such as p53, p16, p21, p27, TRAIL R1, cytochrome c, Apaf-1, caspase-3, caspase-7, caspase-8, and caspase-9 proteins; inhibited COX-2, as well as decreased levels of malondialdehyde (MDA) and enzymatic activity of antioxidants in eliminating free radicals. However, in most conducted studies, no clear mechanism of the plants' effect has been observed, which may further be investigated.

Allium sativum L., *Zingiber officinale* Roscoe, *Annona muricata* L., and *Camellia sinensis* (L.) Kuntze have been conducted in clinical trials. Soursop is the only plant with data for all three tests—*in vitro*, *in vivo*, and clinical trials. Four plants were able to reduce the size, frequency, and incidence or recurrence of colon adenoma. Based on the safety evaluation, the dose of the

four plants was safe for consumption and tolerable, but there were still side effects in a small proportion of patients.

CONCLUSION

This study has examined the current evidence of Indonesian plants that have chemoprevention of CRC. Furthermore, it could be a strategy to identify the compounds with anticancer effects. About 77 plants from 47 families cultivated in Indonesia were identified as candidates for developing chemopreventive agents for CRC. Various group compounds of the plants revealed anticancer on CRC. However, bioassay-guided approaches are required to identify major active compounds of the plants responsible prevent CRC. In clinical studies, *A. sativum* L., *Z. officinale* Roscoe, *A. muricata* L., and *C. sinensis* (L.) Kuntze were able to reduce the risk of progression or recurrence of colon adenoma. The doses of the four plants were safe and tolerated. However, few individuals still had adverse effects. Future strategies can also focus on a clinical trial in other plants to evaluate the safety and efficacy in the prevention and treatment of cancer.

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AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

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The authors declare that they have no conflicts of interest.

ETHICAL APPROVALS

This study did not involve animals and humans, so ethical clearance is not required.

DATA AVAILABILITY

All data generated and analyzed are included in this research article.

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