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-

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![Flow chart of study selection process.](image-url)
| Plant name (Indonesian name)                  | Family      | Extract(s) and part(s) used   | Dose            | Model(s)                        | Mechanisms                                                                 | Signaling pathways | Experiment | Reference               |
|---------------------------------------------|-------------|-------------------------------|-----------------|---------------------------------|-----------------------------------------------------------------------------|--------------------|------------|-------------------------|
| 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 multierypt aberrant crypt growth | Bel-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 | Bel-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 | (Anuselvan et al., 2012) |
| Allium sativum L. (Bawang putih)            | Alliaceae   | Hydroalcohol bulbous 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; chlorofom; 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                      |
|----------------------------|--------|-----------------------------|---------------|----------|----------------------------------------------------------------------------|---------------------|------------|---------------------------------|
| **Andrographis paniculata** (Burm. f.) Nees (Sambiloto) | Acanthaceae | Ethanol herb extract | 250 and 500 mg/kg | DMH-induced ACF of Sprague-Dawley rats | Suppress the formation and multiplicity of ACF | PCNA | In vivo | (Ansil et al., 2013) |
| **Annona muricata L. (Sirsak)** | Annonaceae | Ethanol leaves extract | 15.625–400 μg/ml | COLO-205 | Antioxidant activity; reduction number of ACF | PCNA | In vivo | (Al-Henhena et al., 2014) |
| | | | 5–300 μg/ml | WiDr | Inhibiting the proliferation of cells | Caspase-3 | In vitro | (Abdullah et al., 2017) |
| | | 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 | Bel-2 | 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 Bel-2 | In vivo | (Moghadamtousi et al., 2015) |
| **Annona squamosa L. (Srikaya)** | Annonaceae | Methanol, acetone, and aqueous leaves fraction | 100 μg/ml | LoVo and HCT-116 | Inhibiting the growth and migration of cells; inducing apoptosis cell death | | In vitro | (Al-Nemari et al., 2020) |
| **Arctangelisia flava (L.) Merr. (Akar kuning)** | Menispermacae | Ethanol stems extract | 31.25–500 μg/ml | WiDr | Inhibit cells growth | | In vitro | (Mutiah et al., 2020) |
| **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                      |
|-----------------------------|-----------|----------------------------|-----------------------|-----------|----------------------------------------------------------------------------|-------------------------------------|------------|--------------------------------|
| *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)          |
| *Brassica javanica* (L.) Merr. (Buah makassar) | Simaroubaceae | Ethanol fruit extract | 25–100 µg/ml         | HT-29     | Induce cell apoptosis via mitochondrial-dependent and -independent event  | Bel-2  | In vitro  | (Bagheri et al., 2018) |
| *Caesalpinia sappan* L. (Secang) | Caesalpiniaceae | Ethanol heartwood extract | 2.5–30 µg/ml         | WiDr      | Inhibit viability of cells                                                | Cytochrome-c, Bax, Bad, Caspase-9  | 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 |
|-----------------------------|--------|-----------------------------|------|----------|------------|-------------------|------------|-----------|
| *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 | Blocking cells migration; reducing invasive cells; inhibiting adhesion of cells | Deferoxamine | In vitro | (Astuti and Primasari, 2020) |
| *Coix lacryma-jobi* L. (Jali) | Poaceae | Aqueous herb extract | 0.25–10 mg/ml | HCT-116 | Inhibiting proliferation of cells; induction apoptosis cell death | Bcl-2, p53, Caspase-9 | 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 | 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; G₀/G₁ cell-cycle arrest; induction apoptosis | | In vitro | (Hong et al., 2016) |
| *Curcuma purpurascens* Blume (Temu tis) | Zingiberaceae | Dichromemthane 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) |
| *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 | | | (Rouhollahi et al., 2015b) |

*Note: ACF stands for adenomatous colorectal polyps.*
| Plant name (Indonesian name) | Family            | Extract(s) and part(s) used | Dose              | Model(s)                                                                 | Mechanisms                                                                                      | Signaling pathways | Experiment | Reference          |
|-----------------------------|-------------------|-----------------------------|-------------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|--------------------|------------|-------------------|
| Dendrophthoe pentandra (L.) Miq (Kemladean) | Loranthaceae      | 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   | (Endharti et al., 2016) |
| Diospyros kaki L.f. (Kesemek) | Verbenaceae       | Ethanol calyx extract       | 125, 250, and 500 mg/kg | AOM- and DSS-induced ACF of Balb/c mice                                | Preventing proliferation of cells; inhibition of S phase                                          | MPO                | p53       | In vivo (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         | Ethanol herb 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              | 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 |
|-----------------------------|--------|-----------------------------|------|----------|----------------------------------------------------------------------------|---------------------|------------|-----------|
| *Glycyrrhiza glabra* L.    | Fabaceae | Ethanol root extract      | 200 µg/ml | HT-29  | Inhibiting proliferation of cells; induction of apoptosis cells           | HSP90             | In vitro  | (Nourazarian et al., 2016) |
| *(Akar manis)*              |        |                             |      |         |                                                                             |                     |            |           |
| *Gnetum gnemon L.*          | 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) |
| *(Melinjo)*                  |        |                             |      |         |                                                                             |                     |            |           |
| *Graptophyllum pictum* L.  | Acanthaceae | n-Hexane leaves fraction  | 5–2,000 µg/ml | WiDr  | Inhibit proliferation of cells                                           |                     | In vitro  | (Amin et al., 2020)     |
| *(L.) Griff (Daun wungu)*   |        | Ethanol leaves extract    | 12.5–500 µg/ml | WiDr  | Inhibit proliferation of cells                                           |                     | In vitro  | (Da’i, 2015)           |
| *Guazuma ulmifolia L.*     | Malvaceae | Ethanol leaves extract     | 50–1,000 µg/ml | WiDr  | Inhibit proliferation of cells                                           |                     | In vitro  | (Nurulita et al., 2011) |
| *(Jati belanda)*            |        | Ethanol leaves extract    | 250 and 500 mg/kg | WiDr  | Inhibit proliferation of cells                                           |                     | In vitro  | (Shwter et al., 2014)   |
| *Gynura procumbens* L.     | Asteraceae | Ethyl acetate leaves fraction | 50–1,000 µg/ml | WiDr  | Inhibit proliferation of cells                                           |                     | In vivo   |           |
| *(Lour. Merr. (Sambung nyawa))|        | Ethanol leaves extract    | 250 and 500 mg/kg | WiDr  | Inhibit proliferation of cells                                           |                     | In vivo   |           |
| *Hedyotis corymbosa* L.    | Rubiaceae | Ethanol herb extract       | 10–125 µg/ml | WiDr  | Inhibit proliferation of cells; G1/S cell-cycle arrest                     |                     | In vitro  | (Meifasari et al., 2016) |
| *(Rumput mutiara)*          |        |                             |      |         |                                                                            | Pim-1              |            |           |
| *Hedyotis diffusa* Willd.  | 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                | Bax, PARP, Caspase-3, Caspase-9 | In vitro | (Feng et al., 2017)     |
| Plant name (Indonesian name) | Family | Extract(s) and part(s) used | Dose | Model(s) | Mechanisms | Signaling pathways | Experiment | Reference |
|-----------------------------|--------|-----------------------------|------|----------|------------|-------------------|------------|----------|
| **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; inhibit sonic Hedgehog and angiogenesis | <AQ> | 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 | Bcl-2, COX-2, iNOS, eNOS, HIF-1α, VEGF-A, VEGFR2 | In vitro | (Wong et al., 2014) |
| **Houttuynia cordata** Thunb. (Amis-aminan) | 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 | In vitro | (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 cells | Bcl-2 | 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               |
|-----------------------------|--------------|-----------------------------|-----------------|---------------------------------|-----------------------------------------------------------------------------|--------------------|-----------------|------------------------|
| *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                               | MsrSOD             | In vitro       | (Lauricella et al., 2019) |
| *Melaissa officinalis* L. (Lemon balm) | Lamiaceae   | Aqueous leaves extract      | 250, 375, and 500 µg/ml | HCT-116 | Inhibit viability of cells; G/M cell-cycle arrest; inhibit migration; promote apoptosis | N-cadherin        | In vitro       | (Kuo et al., 2020)     |
|                           |              | Hydroalcoholic leaves extract | 0.5–1,000 µg/ml | HT-29 and T84                       | Inhibiting proliferation of cells; G/M cell-cycle arrest                  | 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                                              | Caspase-3, Bcl-2   | 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 | Caspase-3, Bax     | In vitro       | (Li et al., 2012)      |
| *Moringa oleifera* Lam. (Kelor) | Moringaceae | Ethanol bark and leaves extract | 250 and 500 µg/ml, 500 μg/ml | HCT-8    | Inhibiting proliferation of cells; inhibiting motility and colony formation; G/M cell-cycle arrest | PCNA, iNOS, COX-2  | In vivo        | (Al-Asmari et al., 2015) |
|                           |              | Aqueous seed extract        | 6%              | AOM-induced ACF of Sprague-Dawley rats | Decrease incidences and multiplicities of tumor                           | Caspase-3, Caspase-7 | 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                                                | Caspase-3, Caspase-7 | 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                                              | Survivin           | In vivo        | (Nasir et al., 2017)   |
|                           |              | Ethanol leaves extract      | 150–600 µg/ml  | HT-29 and Caco-2          | Inhibit proliferation of cells; inhibit colony growth; induce mitotic arrest and apoptosis | Caspase-3, Caspase-7 | In vitro       | (Benhalilou et al., 2019) |
| *Origanum majorana* L. (Marjoram) | Lamiaceae  | Ethanol leaves extract      | 3.625–100 µg/ml | HCT-116          | Suppress angiogenesis of cells                                            |                    | In vitro       | (Ahamed et al., 2012)  |
|                           |              | 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                                           |
|---------------------------------------------------|-----------------|-----------------------------------|--------------------|--------------------------------------------------------------------------|---------------------------------------------------------------------------|--------------------|------------|-----------------------------------------------------|
| *Phaleria macrocarpa* (Scheff.) Boerl. (Mahkota dewa) | Thymelaeaceae   | Ethanol leaves extract            | 100 and 200 mg/kg  | HCT-116 cells inoculated into BALB/c mice (TXM)                         | Suppressing tumor growth; antiangiogenicity                               |                    | In vivo    | (Rakasiwi et al., 2020)                            |
| *Phyllanthus reticulatus* Poiret. (Mangisan)       | Phyllanthaceae  | Aqueous and ethanol herb extract  | 7.8–1,000 μg/ml    | HT-29                                                                    | Inhibit proliferation of cells                                            | Bel-2              | In vitro   | (Aarthi and Babu, 2017)                            |
| **Physalis angulata** L. (Cepukan)                 | Solanaceae      | Ethanol herb extract              | 7.81–1,000 μg/ml   | WiDr                                                                     | Inhibit viability of cells                                               |                    | In vitro   | (Djananjega, 2008)                                |
| *Piper betle* L. (Sirih hijau)                     | Piperaceae      | Aqueous leaf extract              | 100–1,200 μg/ml    | HCT-116 and HT-29                                                        | Inhibiting proliferation of cells; S and G/M cell-cycle arrest; inducing apoptosis | 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)                             |
| **Pogostemon cablin** Benth. (Nilam)               | Lamiaceae       | Aqueous leaves extract            | 5.83–93.2 μg/ml    | HT-29                                                                    | Inhibiting viability of cells; G1/G0, cell-cycle arrest                   |                     | In vitro   | (Chien et al., 2020)                              |
| **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                  |
|-----------------------------|----------------------|----------------------------|--------------------|----------------------------------------------|-------------------------------------------------|--------------------------------------------------------|------------|---------------------------|
| *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 ↓ Decrease | 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 | Bcl-2 Increase | 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 of cells; decrease 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* (Wild.) 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 viability of cells; promoting apoptosis; G cell-cycle arrest | Bcl-2 Increase, Caspase-3, Caspase-9 | In vitro | (Mohammadi et al., 2016)  |
|                             |                      | Diethyl ether seed extract | 30 ml/kg          | AOM-induced colon carcinogenesis of Wistar rats | Suppress aberrant crypt foci, adenoma, and adenocarcinoma formation | CEA ↑ Increase, COX-2 | In vivo | (Uyar et al., 2021)       |
| *Voacanga foetida* (Blume) Rolle (Tampa budak) | Apocynaceae          | Ethyl acetate leaves extract | 0.1, 0.5, and 1 µg/ml | HTB-38                                       | Inhibit viability of cells                        | In vitro | (Susan ty 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, SW480, and LoVo                     | Inhibit viability of cells; promote apoptosis  | ATF3 Increase | 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 | In vitro | (Park et al., 2014b)     |
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 (Ruvnov 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, contained crude drug treatment on colon tumorigenesis are presented in Table 2.

### Table 2

| Plant name (Indonesian name) | Family | Extract(s) and part(s) used | Dose | Model(s) | Mechanisms | Signaling pathways | Experiment | Reference |
|------------------------------|--------|-----------------------------|------|----------|------------|-------------------|------------|-----------|
| 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 focus; 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. |
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 (Cerar, 2010).

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.

| Plant name                          | Family name | Subject                        | Type of study                          | Formulation/Dose                               | No. of subjects | Length of study | Outcome                                      | 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 acacetogenin)/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)                         |

Table 2. Human studies of plants and colon tumorigenesis.
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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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.

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

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

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