Chapter 18

Studies of Malaysian Plants in Prevention and Treatment of Colorectal Cancer

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Additional information is available at the end of the chapter

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Abstract

Incidence rates vary 10-fold globally for colorectal cancer (CRC). Asia has lower rates than Western countries, but as the Western life-style becomes more prevalent in economically developing Asian countries, rates are increasing. Clinical therapy has improved over the last few decades, and national screening programmes are a proven and effective means of reducing mortality; chemoprevention through diet and life-style choices may provide additional value. Diet has strong associations with the aetiology of CRC, considerable epidemiological evidence exist that fruits and vegetables are associated with reduced risk of CRC. There is also extensive experimental evidence that phytochemicals from fruit and vegetables can modulate pathways of carcinogenesis. In this chapter, we consider Malaysia specifically, with its rich ethnopharmacological heritage and megabiodiversity; Malaysian natural compounds may be a source of potentially chemo-protective with relevance to CRC.

Keywords: colon cancer, in vitro, Malaysia, plants, anticancer

1. Introduction

Botanically, Malaysia is one of the most bio-diverse countries in the world with more than 23,000 plant species recorded [1]. Many components of these plants are traditionally used for flavour and fragrances as well as for medicinal purposes. In line with bio-prospecting trend to find new pharmaceutical lead compounds for medical applications; researchers from local academic and research institutions within Malaysia have initiated investigations of the bioactive properties of various native plants. In Malaysia, colorectal cancer is the second most frequent cancer after

breast cancer [2]. The aim of this review is to collate data and conclusions from recent studies undertaken on indigenous Malaysian plants with a view toward prevention and/or treatment of colorectal cancer (CRC).

2. Epidemiology of CRC

The geographical distribution of CRC differs significantly (~10-fold) across the world with the highest incidence rates in Australia/New Zealand (age-specific rate; ASR 44.8 and 32.2 per 100,000 in men and women, respectively), North America (ASR 30.1 and 22.7 per 100,000), Europe (ASR 37.3 and 22.7 per 100,000), and Japan (ASR 42.1 and 23.5 per 100,000). The lowest incidence rates occur in West Africa (ASR 4.5 and 3.8 per 100,000) although in this case, under-reporting is likely due to incomplete coverage by registries [2].

The global rise of incidence and mortality rates attributable to cancer is likely due to the ageing population, with incidence predicted to increase to 22.2 million cases globally by 2030 [3]. The cancer pattern among countries exhibits a strong societal and economic influence, where countries with a low human development index (HDI) (composite measure of life expectancy, education, and gross domestic product per head) tend to have higher levels of infection-related cancers (i.e., cervical) compared to medium and high HDI countries where the cancer burden is more commonly related to reproductive, dietary, and hormonal factors (e.g., lung, breast, and colorectal) [3]. As such, it is clear that CRC incidence rates increase in accordance with a country's income [4].

Asia as a whole consists mainly of developing countries and as such, incidence rates of CRC (ASR 16.5 and 11.1 per 100,000 in men and women, respectively) are noticeably lower than for the mainly developed countries of Europe—both in terms of incidence and in mortality (**Table 1**). However, cancer incidence and mortality in Asia is likely to rise over the next 20 years, due in part to a rapid population expansion that will not be experienced by Western countries. This increase will clearly impact on the health care burden associated with cancer, and also quality of life across Asia as a whole. Ng and colleagues [4] recently considered the wide variation in cancer incidence and mortality across Asia with respect to cancer survival, defining it in terms of mortality to incidence ratios (MIR = 1 no effect on survival). Although cancer incidence is lower in Asia, cancer survival is higher in Western countries as the MIRs are lower. Moreover, while Eastern and Western Asia have a higher incidence of CRC compared to South-Eastern and South-Central Asia, the pattern for survival is reversed in that the latter two regions have poorer survival than Western and Eastern Asia [4]. In Malaysia (South Eastern Asia), CRC is the second most common malignancy after breast cancer, while incidence rates exceed that of China, cancer survival is similar. By contrast, in Japan, both incidence and survival are higher.

2.1. CRC pathogenesis

The majority of colorectal malignancies occur as sporadic forms that appear to arise from benign adenomatous polyps, with carcinomas emerging slowly over a period of 10–20 years [6–9]. Epidemiological data indicate that incidence and mortality rates of colorectal cancers

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(CRC) are greatly influenced by age rather than by gender. The majority of cases are detected in individuals over the age of 60 [10], with 55% of cases occurring in more developed regions in contrast to 52% of all CRC deaths which occur in the less-developed regions of the world, reflecting poorer survival. For individuals diagnosed with CRC, it has been determined that the 5-year survival rate is approximately 50–60% [11] and that survival among CRC patient is improved if WCRF/AICR lifestyle guidelines on physical activity, body fatness, and diet are adhered to [12]. The age-dependent increase in CRC development is associated with a multi-step oncogenesis process and a number of histological stages, reflecting the accumulation of genetic errors in somatic cells over time. Sporadic CRC is currently thought to arise via 1 of 3 identified molecular pathways (Micro Satellite instability—MSI, Chromosomal Instability—CIN and CpG island methylator phenotype—CIMP) depending upon the individual's complement of gene alterations [13]. Conversely, the inheritance of germline mutations may also result in development of neoplasms at an early age, with approximately 5% of CRC cases being due to inherited single-gene syndromes such as familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC) [14]. It is estimated that as much as 12–35% of colon cancers can be explained by heritable factors, but known single-nucleotide polymorphisms appear to explain only a small proportion of these [15].

The high degree of molecular heterogeneity present in CRC is reflected by the effectiveness of chemotherapeutic regimes; however, the clinical significance of the majority of these individual molecular alterations is still to be fully determined [16]. From a treatment perspective, early-stage CRC is managed by surgical resection and advanced CRC with a combination of chemotherapy and surgery. Most chemotherapeutic regimes use 5-Fluorouracil (5-FU) as the main cytotoxic agent and this is commonly administered in conjunction with oxaliplatin for adjuvant therapy for high-risk stage II/stage III CRC, and with either oxaliplatin or irinotecan for metastatic CRC. Furthermore, the addition of bevacizumab-based chemotherapy (a vascular endothelial growth factor (VEGF)-targeted agent) has proven to be more effective than cytotoxic chemotherapy alone for the treatment of metastatic CRC [17].

While there is no doubt that CRC treatments have advanced over the last decade, improvement in disease outcome has been more modest relative to the increase in treatment costs. Thus, population screening is an important and cost-effective strategy given the improved prognosis with early detection [18]. The pathogenesis of CRC makes it very well suited to population screening especially given the correlation between disease stage and mortality. It is clear that the detection and the removal of cancer precursors can reduce CRC incidence and mortality and effective detection of CRC allows for less invasive treatment with a better prognosis. As is to be expected, a large variation exists globally in the implementation of screening programmes both in terms of strategy used (organised vs opportunistic) and standards applied (diagnostic test, detection threshold), with implementation more common in Western countries [19]. Europe for the most part has implemented an organized screening programme, while the USA operates an opportunistic approach. In Asia, several countries have already developed organized programmes including Japan, Korea and, to a lesser extent, China. As yet, however, Malaysia has no organized screening in place. As cancer incidences are likely to continue to rise, screening programmes will necessarily become more of an issue for low

resource countries. Moreover, as cancer pattern types change, there will arise a need to developed tailored approaches [19].

Region	Incidence		Mortality		5-year prevalence	
	Number	ASR (W)	Number	ASR (W)	Number	Prop
Australian/New Zealand	18887	38.2	5489	10	54266	245.4
Europe	447136	29.5	214866	12.5	1203943	192.3
North America	158169	26.1	63465	9.4	486650	172.9
Asia	607182	13.7	331615	7.2	1493520	47
Asian region						
Eastern Asia (EA)	421343	18.4	207716	8.4	1130066	87.1
Western Asia (WA)	27140	14.8	15306	8.4	62162	37.5
South Eastern Asia (SEA)	69016	12.5	43234	7.9	158845	35.7
South Central Asia (SCA)	89683	6.1	65359	4.4	142447	11.3
Country						
Australia	15869	38.4	4168	9	45622	245.8
Japan (EA)	112675	32.2	49345	11.9	384877	350.8
UK	40755	30.2	16202	10.7	104047	200.5
Malaysia (SEA)	4539	18.3	2300	9.4	9714	47
China (EA)	253427	14.2	139416	7.4	583054	52.7
Saudi Arabia (WA)	2047	11.6	1094	6.6	4486	22.3
India (SCA)	64332	6.1	48603	4.6	86650	9.8

Incidence and mortality data for all ages. Five-year prevalence for adult population only. ASR (W) and proportions per 100,000 persons per year. The ASR is a weighted mean of the age-specific rates. Adapted from [5].

Table 1. Incidence and mortality rates (estimated, all sexes) for colorectal cancer, globally and within Asia and selected regions.

2.2. Diet and CRC

The relatively recent increase in CRC incidence in Japan (Eastern Asia) and in urbanized regions of China (Eastern Asia) is of significant concern [20] and is thought to be due to the adoption of a more a Western lifestyle and diet [21]. Diet plays a central role in CRC pathogenesis, as those rich in saturated animal fat, and red meat (especially processed meat) [22] together with alcohol intake [23] and smoking [24] have been positively associated with colorectal neoplasia. Fruit and vegetable consumption is associated with a reduction in the risk of CRC [25], and this concept is supported by a large body of case-control studies, although results from cohort or prospective studies are less convincing [26]. Nevertheless, the protective effects of fruits and vegetables against colorectal cancer are attributed to the large number of

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bioactive phytochemicals present within them [27], comprising mainly plant polyphenolic secondary metabolites [28] and plant structural and storage polysaccharides which make up dietary fiber [29, 30]. These various plant components or natural products are found within a range of indigenous Malaysian fruit and vegetables, and thus may potentially play a role in chemoprevention for CRC.

3. Natural product research in Malaysia

Natural products include a large and diverse group of substances produced by a variety of sources including marine organisms, bacteria, yeasts, fungi, and plants [31]. Research on natural products has focused primarily on the chemical properties, biosynthesis, and biological functions of secondary metabolites [32]. Natural products, in particular plants, have been used in traditional medicine and health practice. The World Health Organization has acknowledged traditional medicine as a contributor to achieve health care objectives [33] and Malaysia, blessed with its megabiodiversity and rich ethnopharmacological heritage, has been observed to elegantly capitalize on these attributes with a view toward boosting the wealth and wellness of its population [34].

In late 2010, the Malaysian government launched the Economic Transformation Programme (ETP), which focuses on 12 National Key Economic Areas (NKEAs). The Agriculture sector, under the purview of the Ministry of Agriculture (MoA) is one of the NKEA-identified areas where the Entry Point Project 1 (EPP1) is focused on high-value herbal products. The MoA has overseen the establishment of five R&D clusters, which focus on, respectively, discovery, crop production, and agronomy, standardization and product development, toxicology/pre-clinical and clinical studies, and processing technology. The initial phase of this EPP was focused on ensuring the supply of five main local herbs, namely Tongkat Ali (*Eurycoma longifolia* Jack), Misai Kucing (*Orthosiphon aristatus* (Blume) Miq.), Hempedu Bumi (*Andrographis paniculata* (Burm.f.) Nees), Dukung Anak (*Phyllanthus niruri* L.) and Kacip Fatimah (*Marantodes pumilum* (Blume) Kuntze (*syn. Labisia pumila* (Blume) Mez). Subsequently, six more herb species were added to the project, including Mengkudu (*Morinda citrifolia* L.), Roselle (*Hibiscus sabdariffa* L.), Ginger (*Zingiber officinale*), Mas Cotek (*Ficus deltoidea* Jack), Belalai Gajah (*Clinacanthus nutans* (Burm.f.) Lindau) and Pegaga (*Centella asiatica* (L.) Urb) [35]. In 2014, eight products developed through the EPP 1 underwent pre-clinical trials. It is estimated that commercialization of the identified herbs will contribute MYR2.2 billion to the Gross National Income (GNI) by 2020 [35].

In Malaysia, research on natural products including the EPP-listed local herbs described above is being undertaken by research centers and institutions of higher learning (**Table 2**). Nevertheless, research in this area is also being carried out by various independent research groups in the local academia.

Entities	Institutions
Advanced Medical and Dental Institute	Universiti Sains Malaysia (USM)
Atta-ur-Rahman Institute for Natural Product Discovery	Universiti Teknologi MARA (UiTM)
Bioresource and Drug Discovery Research Group (BDD), Faculty Science and Natural Resources (FSSA)	Universiti Malaysia Sabah (UMS)
Centre For Natural Products And Drug Research (CENAR)	Universiti Malaya (UM)
Drug Discovery and Development Research Group (under purview of the Natural Products Cluster)	Universiti Kebangsaan Malaysia (UKM)
Institute of Bioproduct Development (IBD)	Universiti Teknologi Malaysia
Laboratory of Natural products, Institute of Bioscience	Universiti Putra Malaysia (UPM)
Natural Medicine Products Centre (NMPC)	International Islamic University Malaysia (IIUM)
Natural Product and Drug Discovery Centre (NPDC)	Malaysian Institute of Pharmaceuticals and Nutraceuticals (IPharm)
Natural Product Lab, Institute of Marine Biotechnology	Universiti Malaysia Terengganu (UMT)
Natural Products Division	Forest Research Institute Malaysia (FRIM)

Table 2. Entities involved in natural product research and development in Malaysia.

4. Studies of the effect of Malaysian plants on colon cancer

It has been estimated that around 1200 medicinal plants have potential pharmaceutical value [1]. Many of these species have been scientifically investigated by researchers seeking to provide evidence of effectiveness toward different diseases such as cancer, diabetes, arthritis, heart diseases, and many others. However, work on the effects of Malaysian plants on colon cancer specifically has been very limited (**Tables 3** and **4**). Nonetheless, several observations may be made on work undertaken to date that allow trends to be identified for the future of such work.

It is clear that there is no focused approach on any particular species, and most of the studies were conducted at the early stage of screening for anti-cancer effects with little in the way of continued development thereafter. This work includes cytotoxicity screening of crude extracts or compounds derived from solvent fractions against several types of cancer using *in vitro* cell line-based experiments. While the species investigated are edible herbs and fruit plants, in several instances, the parts of the plant investigated may not be commonly consumed as food. For instance, Moghadamtousi et al. [36] studied the leaf of soursop plant, rather than the more commonly consumed fruits, while Aisha et al. [38] investigated the rind of mangosteen fruit instead of the flesh. To this end, selection of species seems to be based on ethnomedicinal evidence within local communities and capitalizing upon the novelty aspect in that the species (or parts of plants) have not been investigated by other groups. The use of inedible plant parts may be also be related to the zero waste and health to wealth concepts where all parts of plants

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are considered potential biomass to be exploited. As such, materials from inedible parts of plants may be more cost-effective to be used. Furthermore, the majority of studies appear to be "isolated studies" with lack of continuing development as stated above, which may perhaps be due to lack of funding and proper planning for future work including networking. The lack of funding may also correspond to lack of facilities and equipment required to do further in depth robust work.

Plant and part of plant used	**Common name**	**Compound/ extract tested**	**Type of study**	**Details/IC_{50}**	**Reference**
Annona muricata L. (Leaf)	Graviola, soursop; [a]durian belanda	Ethyl acetate extract	*In vitro* HCT 116, HT29 and CCD841 cell lines	*In vitro* cytotoxicity IC_{50} = 4.29 ± 0.24 μg/ml (HT29) IC_{50} = 3.91 ± 0.35 μg/ml (HCT116) IC_{50} = 34.24 ± 2.12 μg/ml (CCD841) 5-Fluorouracil (positive control) IC_{50} = 1.10 ± 0.11 μg/ml (HT29) IC_{50} = 0.90 ± 0.09 μg/ml (HCT116) The extract also showed cell cycle arrest at G_1, induction of apoptosis, anti-migration and anti-invasive effects.	[36]
Annona muricata L. (Leaf)	Graviola, soursop; [a]durian belanda	Ethyl acetate extract	*In vitro* HT29 and CCD 841 cell lines. *In vivo* AOM-induced colon cancer in rats	*In vitro* cytotoxicity HT29 IC_{50} = 5.72 ± 0.41 μg/ml (12 h) IC_{50} = 3.49 ± 0.22 μg/ml (24 h) IC_{50} = 1.62 ± 0.24 μg/ml (48 h) CCD 841 IC_{50} = 64.32 ± 3.76 μg/ml (12 h) IC_{50} = 47.10 ± 0.47 μg/ml (24 h) IC_{50} =32.51 ± 1.18 μg/ml (48 h) Aberrant Crypt formation after 2 weekly injections of extract. 250 mg/kg = 61.2% inhibition 500 mg/kg = 72.5% inhibition 5-FU = 79.5% inhibition	[37]
Garcinia mangostana (Fruit rind)	Mangosteen; [a]manggis	Xanthone (81% α-mangostin and 16% γ-	*In vitro* HCT 116 cell line *In vivo* Subcutaneous tumor of	*In vitro* cytotoxicity 1) IC_{50} = 6.5 ± 1.0 μg/ml 2) IC_{50} = 5.1 ± 0.2 μg/ml 3) IC_{50} = 7.2 ± 0.4 μg/ml IC_{50} of Cisplatin (positive	[38]

Plant and part of plant used	Common name	Compound/ extract tested	Type of study	Details/IC_{50}	Reference
		mangostin) from toluene extract of the fruit α-mangostin γ-mangostin)	HCT116 on nude mice	control) = 6.1 ± 0.2 μg/ml The extract also showed induction of apoptosis, anti-tumorigenicity and up-regulation of MAPK/ERK, c-Myc/Max, and p53 cell signalling pathways *In vivo* Xanthones extract caused significant growth inhibition of the subcutaneous tumor	
Garcinia mangostana (Fruit rind)	Mangosteen; [a]manggis	Hexane and ethyl acetate (Other extracts produced, butanol and methanol)	*In vitro* Caco-2 cell line (also tested on other cells KB and PBMC)	*In vitro* cytotoxicity IC_{50} = 13.0 ± 3.8 μg/ml (Hexane) IC_{50} = 8.1 ± 0.1 μg/ml (Ethyl acetate) IC_{50} of Tamoxifen positive control = 4.0 ± 0.4 μg/ml	[39]
Garcinia mangostana (Fruit rind)	Mangosteen; [a]manggis	α-mangostin β-mangostin γ-mangostin hexane extracts	*In vitro* DLD-1 cells	All three extracts showed anti-proliferative effects at 20 μM.	[40]

Table 3. Studies of anticancer effects of plant materials obtained from fruit trees in Malaysia.

Plant and part of plant used	Common name	Compound/extract tested	Type of study	Details/IC_{50}	References
Alpinia mutica (Rhizome)	[a]Tepus	Methanol and fractionated extracts (hexane, ethyl acetate and water)	*In vitro* HT 29 and HCT 116 cell line (also tested on other cell lines; KB, CasKi, MCF-7, A549 and MRC-5)	Hexane extracts showed IC_{50} of 36.1 ± 1.1 μg/ml (HCT116) and 47.4 ± 1.6 μg/ml (HT29) Ethyl acetate extracts showed IC_{50} of 20.4 ± 3.2 μg/ml (HCT116) and 24.2 ± 0.04 μg/ml (HT29) Methanol and water extracts showed IC_{50} of more than 100 μg/ml IC_{50} of doxorubicin (positive control) = 0.24 ± 0.04 μg/ml (HCT116) and 0.33 ± 0.03 μg/ml	[41]

Plant and part of plant used	Common name	Compound/extract tested	Type of study	Details/IC_{50}	References
				(HT29)	
Casearia capitellata (Leaf) *Baccaurea motleyana* (fruits and peel) *Phyllanthus pulcher* (Leaf, stem and root) *Strobilanthus crispus* (Leaf, flower)	[a]Simmilit matangi [a]Rambai [a]Naga buana [a]Pecah kaca/Pecah beling/ Pokok pecah/Jin batu/	Hexane, dichloromethane, ethyl acetate and methanol extracts, respectively	*In vitro* HT29 cell line (also tested on other cell lines; MCF-7, DU-145 and H460)	DCM extract of *P.pulcher* root showed the lowest IC_{50} among the extracts tested against HT29 cells (IC_{50} = 8.1 ± 0.5 μg/ml)	[42]
Curcuma mangga (Rhizome)	[a]Temu pauh/ Kunyit mangga	Crude methanol and fractionated extracts (hexane, ethyl acetate)	*In vitro* HT 29 and HCT 116 cell line(also tested on other cell lines; KB, CasKi, MCF-7, A549 and MRC-5)	Extracts showed the IC_{50} between 29.4 ± 0.2 and 36.8 ± 3.8 μg/ml against HCT116 cells Extracts showed the IC_{50} between 17.9 ± 0.3 and 22.0 ± 1.1 μg/ml against HT29 cells IC_{50} of doxorubicin (positive control) = 0.24 ± 0.04 μg/ml (HCT116) and 0.33 ± 0.03 μg/ml (HT29) Isolated compounds from the extracts also showed high cytotoxicity effects towards both cell lines (between 6.3 ± 0.26 and 14.9 ± 0.40 μg/ml) Several isolated compounds from the extracts also showed considerable cytotoxicity effects against the cancer cells	[43]
Curcuma mangga (Rhizome)	[a]Temu pauh/	Hexane and ethyl acetate extracts.	*In vitro* HT29 and CCD-18Co	*In vitro* cytotoxicity (72 h) Hexane: IC_{50} = 17.9 ± 1.2 μg/ml (HT29)	[44]

Plant and part of plant used	Common name	Compound/extract tested	Type of study	Details/IC_{50}	References
	Kunyit mangga			IC_{50} = 45.7 ± 1.0 μg/ml (CCD-18Co) Ethyl acetate: IC_{50} = 15.6 ± 0.8 μg/ml (HT29) IC_{50} = 46.5 ± 0.1 μg/ml (CCD-18Co)	
Pereskia bleo (Kunth) DC. (Cactaceae) (Leaf)	[a]Jarum tujuh bilah	Compounds from ethyl acetate fraction • Dihydroactinidiolide • β-sitosterol • 2,4-di tert butyl phenol • α-tocopherol • Phytol	*In vitro* HCT 116 cell line (also tested on other cell lines; KB, CasKi, MCF-7, A549 and MRC-5)	Dihydroactinidiolide showed the lowest IC_{50} at 5 μg/ml against HCT116 cells Dihydroactinidiolide showed IC_{50} of 91.3 μg/ml against MRC-5 cells IC_{50} of doxorubicin (positive control) = 0.36 μg/ml (HCT116) and 0.55 μg/ml (MRC-5)	[45]
Piper betle (Leaf)	[a]Sirih	Aqueous extract	*In vitro* HCT 116 and HT29 cell lines	In the presence of the extract, a lower dosage of 5-FU is required to achieve the maximum drug effect in inhibiting the growth of HT29 cells. However, the extract did not significantly reduce 5-FU dosage in HCT116 cells	[46]
Strobilanthus crispus (part of plant used not stated)	[a]Pecah kaca/Pecah beling/ Pokok pecah/Jin batu/	Crude ethanol extract and fractions obtained from column chromatography	In vivo Sprague Dawley (SD) male rats *In vitro* HT29, CCD841	*S. crispus* ethanol extract protects against CRC formation (azoxymethane-induced aberrant crypt foci) in rats Exposure of HT29 and CCD-841 to extract and several fractions (tested between 0 and 500 μg/ml) induced a concentration dependent decrease in cell viability	[47]
Zingiber officinale (rhizome)	Ginger; [a]halia	Ginger: Water-based ultrasonic assisted extraction Honey: Packaged in plastic containers and	*In vitro* HT29 cell lines	*In vitro* cytotoxicity IC_{50} = 5.2 mg/ml (ginger alone) IC_{50} = 80 mg/ml (Gelam honey alone) The combinations of 3 and 4 mg/ml of ginger with 27 and 10 mg/ml	[48]

Plant and part of plant used	Common name	Compound/extract tested	Type of study	Details/IC_{50}	References
		sterilized using gamma radiation		of Gelam honey showed combination index (CI) values of 0.92 and 0.90, respectively, indicating synergistic effects. Cell death in response to the combined ginger and Gelam honey treatment was associated with the stimulation of early apoptosis	
Zingiber officinale (rhizome)	Ginger; [a]halia	Ethanol extract	*In vitro* HCT 116 and HT29 cell lines	Inhibition of proliferation IC_{50} (HCT116) = 496 ± 34.2 μg/ml IC_{50} (HT29) = 455 ± 18.6 μg/ml Induction of apoptosis at 500 μg/ml extract 35.05% (HCT116) and 19.81% (HT29) Ginger extract arrested HCT 116 and HT 29 cells at G0/G1 and G2/M phases with corresponding decreased in S-phase	[49]

[a]Local name in Malay language.
Cell lines: A549 (and human lung carcinoma cell line); CasKi (human cervical carcinoma cell line); CCD841 (normal human colon epithelial cell line); DU-145 (prostate cancer cell line); H460 (lung cancer cell line); HCT116 (colon cancer cell line); HT29 (colon cancer cell line); KB (human nasopharyngeal epidermoid carcinoma cell line); MCF-7 (hormone-dependent breast carcinoma cell line; MRC-5 (non-cancer human fibroblast cell line).

Table 4. Studies of anticancer effects of plant materials obtained herbs and spices in Malaysia.

Some species investigated for their effects against colon cancer in the listed studies have also been investigated for other biological effects. For example, prior to the report by Abdul Malek et al. [43], *Alpinia mutica* was previously reported to have inhibitory activity towards lipid oxidation [50] and anti-bacterial effects against *Bacillus subtilis* and methicillin-resistant *Staphylococcus aureus* (MRSA) [50] in addition to anti-platelet aggregation activities [51].

For *in vitro* work, two types of commercially available colon cancer cell lines, HT29 and HCT116, were used in the majority of studies. However, there is no consistency in the positive controls used in the empirical studies. Some studies include work on CCD841 normal human colon epithelial cells [36, 47], while others include work on 5-Fluorouracil [46, 47], doxorubicin [45], or cisplatin [38] as positive control. Cytotoxic screening results from the studies listed in **Table 3** and **Table 4** showed that effects on colon cancer were only moderate as compared to

other cells lines tested. The follow-up study by Moghadamtousi et al. [37] demonstrated significant decreases in aberrant crypt foci counts in an AOM-induced CRC animal model supporting prior observation *in vitro*. The limited success of *in vitro* studies excluding the aforementioned study may explain the lack of in-depth studies on the effects of the extracts on colon cancer following the screening phase.

The colon cancer cell lines used in the studies differ in their origin, mutation status and metabolic requirements [52]. For example, HT29 cells utilize glucose through the pentose phosphate pathway [53], whereas HCT116 cells have higher requirements for glutamine [52, 54]. In terms of gene expression, HT29 is deficient in expression of p53 [55], while HCT116 cells possess mutations in PI3KCA and KRAS genes which confer constitutive activation of PI3K/AKT and KRAS pathways [56]. Since the two cells lines have different characteristics, the use of such cell lines in preliminary studies is substantial as it can set forth the mechanistic investigations on the effects of the plants against colon cancer.

Although the majority of work was *in vitro*-based preliminary work, Al-Henhena et al. [47] reported both *in vitro* and *in vivo* studies on *Strobilanthus crispus*. Meanwhile, some studies investigated the cytotoxic effects of not only the crude extracts and fractions, but also tested the isolated compounds [38, 40, 45]. Among the studies reported, the same group showed a more thorough investigation of the species selected. Other researchers have combined the selected species with other components to determine their combined effects on colon cancer cells. For instance, Ng et al. [46] looked at the potential effects of *Piper betle* leaf extract to reduce the 5-Fluorouracil dosage required to exert the same cytotoxicity in HT29 and HCT116 cells. Tahir et al. [48] studied the combined effects of *Zingiber officinale* extracts and Gelam honey on viability of HT29 cells. Some researchers have also studied the potential mechanism of the selected species beyond cytotoxicity tests. *Garcinia mangostana* rind extracts showed induction of apoptosis, anti-tumorigenicity, and upregulation of MAPK/ERK, c-Myc/Max, and p53 cell signaling pathways [38] while *Annona muricata* leaf extracts showed cell cycle arrest at G1, induction of apoptosis, anti-migration, and anti-invasive effects [36]. While the follow-up study by Moghadamtousi et al. [37] supports the previous *in vitro* observations with aberrant crypt foci counts significantly reduced by the treatment in an AOM induced CRC animal model. Taken together, studies on Malaysian plants against colon cancer are at different technological levels with, consequently, very limited data to enable a consensus to be made.

Compounding the lack of consensus and technical variability is the fact that choice of journals in which to publish is still very much dependent on funding; thus, publishing in the open access journals with high impact factors can only be afforded by certain groups of researchers. This clearly will have hampered the dissemination of research data as, while it may be beneficial for researchers to reach a wider audience at the early stage of work, this may correspond to having to publish in a low-cost, lower impact journals due to lack of funding. From another perspective, higher impact journals often require more conclusive data, which in turn means more experimental work—early stage work may not meet such journals' publication criteria and may be perceived to be low quality. Therefore, it would be more favorable to have a mechanism to help improve the dissemination of work in order to enhance the overall research and development in the subject area.

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Based on the publications considered in **Tables 3** and **4**, it was also observed that authors did not always report the local names of species investigated. Since these are local plants that may not even have English names, it is to be recommended that this information is included together with full description of the species investigated. This could be one way to present the potential positive effects of the species to a wider scientific community thereby increasing the impact and scientific value of the work. Thus, the correct taxonomy including genus, species and family should be given for accuracy.

5. Conclusion

Some Malaysian plants that show anti-cancer effects towards colon cancer include *Alpinia mutica* (tepus), *Annona muricata* (soursop), *Baccaurea motleyana* (rambai), *Casearia capitellata* (simmilit mantangi), *Curcuma manga* (temu pauh), *Garcinia mangostana* (mangosteen), *Pereskia bleo* (Kunth) (jarum tujuh bilah), *Phyllanthus pulcher* (naga buana), *Strobilanthus crispus* (pecah kaca), *and Zingiber officinale* (ginger).

Nevertheless, much of the scientific evidence is preliminary at best despite the selection of plant species for study based upon ethnomedicinal practices. The introduction of the EPP by the Malaysian government is a commendable effort to raise the value of indigenous Malaysian plants in the pharmaceutical sector. However, a more concerted approach to the work is necessary including a comprehensive review of the existing data in order to fully exploit local plants toward prevention and treatment of colon cancer.

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