ANTI-CANCER PROPERTIES OF LOCALLY AVAILABLE NATURAL PRODUCTS IN MALAYSIA AGAINST COLORECTAL CANCER

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Abstract

Colorectal cancer (CRC) has become a significant worldwide health issue among Malaysians. It has become the second most common disease among men and women, with an increased mortality rate in recent years. CRC cases can be reduced with a healthy diet by increasing natural product intake. However, today most of the commercialized natural products for CRC prevention are imported and costly, which makes 80% of the Malaysian population could hardly afford them due to low and middle household income. Therefore, the present study summarizes the list of local tropical natural products that have remarkable medicinal properties effective on CRC, which are easily accessible for Malaysians, ways to consume them at home, and the economic prospects. This narrative review reviews the latest natural products' properties against CRC, excluding the plants examined in previous studies. The keywords utilized to identify the relevant articles were “Malaysia," "Colorectal Cancer," “Natural products," “Anticancer," "Antidiarrheal," "Mucositis," and "Vomit/Nausea" through PubMed, ScienceDirect, and Google Scholar. **Conclusion:** In conclusion, the locally available natural products have excellent medicinal properties against colorectal cancer with enormous potential medicinal properties in treating CRC and chemotherapy-induced toxicity that Malaysians can use to improve their well-being.

Keywords: Malaysia, Colorectal Cancer, Natural Products, Anticancer, CRC Side Effects

Introduction

Colorectal cancer (CRC) has become one of the deadliest diseases in recent years, with a rapid increase in cases affecting both men and women globally (1,2). It is predicted that by 2030, this disease burden might lead to an upsurge of 60% of mortality cases compared to a recent number of cases (3). Approximately 80% of the cases are sporadic CRC, usually caused by external factors, including a sedentary lifestyle, eating habits, and physical activity (4). Similarly, in Malaysia, CRC cases have been drastically rising in recent years (5), where nearly more than half of the registered CRC cases were detected in the advanced cancer stage (6). The CRC cases in Malaysia are affected mainly by the westernized diet that includes high contents of fat (7) and sugar (8) and minimal fiber content food (9). According to health experts, for the breakthrough of CRC prevention, they strongly suggest practicing a balanced healthy lifestyle by including a daily diet with natural products with high fiber content (7,10,11). Nearly 70% of anti-cancer medications that contain vinca alkaloids, epipodophyllotoxins, taxanes, and camptothecin derivatives (12,13) are derived from natural products such as the *Catharanthus roseus, Tabernaemontana divaricate, Rauvolfia serpentina* (14)*, Podophyllum peltatum* (15)*, Taxus* spp. (16)*, and Camptotheca acuminata* (17). There are many articles previously listed natural products that could

facilitate CRC prevention, such as nuts (almonds, filberts), vegetables (asparagus, broccoli, carrots, potato, brussel sprouts), and fruits (apricot, orange, grapes, strawberries, apples, berries) (8).

However, most listed foods are expensive as they are imported into Malaysia. Moreover, Malaysians are classified into three groups according to their household income; Bottom (B40) (less than RM4850), Middle (M40) (less than RM10,970), and Top (T20) (exceeds RM10,971). Approximately 75% of Malaysian household income falls in B40 and M40 categories (18). Referring to the household income statistics, Malaysians most likely would find it difficult to afford the listed imported natural products by the experts for regular consumption. Malaysia is situated at the earth's equator line, making this country mega biodiversity with thousands of plants that mostly have enormous pharmacological properties. Besides the costly imported natural products diet that could be consumed to prevent CRC and other diseases, Malaysians can provide local natural products diet charts that can aid in CRC prevention and treatment worldwide. This is because many locally available natural products have been proven to have anti-cancer properties against CRC. Hashim *et al*. (2016) have reviewed a few plants that have been widely explored with Malaysian government initiatives (19). However, other plants containing enormous hidden medicinal properties against CRC gained researchers' attention recently and are yet to be reviewed. Moreover, the natural products reviewed in these are still considered in the preliminary research stage in Malaysia.

Therefore, this review article aims to provide a summarized list of natural products that can be easily found and grown in Malaysia and have anti-cancer properties against CRC.

Discussion

Potential Natural products that have Anti-cancer Properties against CRC

According to Hashim *et al*., (2016) *Alpiniamutica* (tepus), *Annona muricata* (soursop), *Baccaurea motleyana* (rambai), *Casearia capitellata* (simmilit mantangi), *Curcuma manga* (temu pauh/kunyit mangga), *Garcinia mangostana* (mangosteen), *Pereskia bleo* (Kunth) (jarum tujuh bilah), *Phyllanthus pulcher* (naga buana), *Strobilanthus crispus* (pecah kaca), *Zingiber officinale* (ginger), *Azadirachta indica* (neem) and *Aloe barbadensis* (Aloe vera). Malaysian plants were widely researched for their anti-cancer properties against colon cancer (9,19,20).

However, apart from these plants, many other plants can be utilized in cancer prevention and treatments, especially CRC, which can be obtained and grown easily in Malaysia weather presented in Table 1.

Vegetables

In vegetables plant family, studies on Moringa oleifera (pokok kelor), Solanum melongena L. (terung), Pachyrhizus tuberosus (sengkuang), Cymbopogon citratus (serai), Abelmoschus esculentus (bendi), Momordica Charantia L.(peria), Psophocarpus tetragonolobus (kacang botol), Parkia speciosa (petai) and Vigna unguiculata (L.) Walp (kacang mata hitam) has shown cytotoxic effects against CRC.

Fruits

In addition, the fruits plant family, *Citrullus lanatus* (tembikai*), Ananas comosus* (nenas)*, Psidium guajava* (jambu batu)*, Euphoria longana Lam* (longan)*, Annona squamosa linn* (pokok nona) and *Nypa fruticans (Wurmb)* (nipah) has shown cytotoxic effect against CRC.

Herbs

In the herbs family, *Piper betle* (sirih)*, Catharanthus roseus* (kemuning cina), *Oenanthe javanica* (selom), *Houttuynia cordata (*pokok hanyir ikan)*, Senna alata* (gelenggang)*, Mentha spicata* (pudina), *Camellia sinensis* (pokok teh) and *Mesua ferrea* (Penaga lilin) have also reported for its cytotoxic effect against CRC by inhibiting the cell proliferation.

All the derivative compounds, plant parts, properties, type of study, and mechanisms of the above natural products are summarized in Table 1. *Catharanthus roseus* plant is reported to have tremendous clinical importance in all these locally available plants. Many Malaysians are unaware that less research has been conducted on this plant in Malaysia. *Catharanthus roseus* has been commercially used as chemotherapy treatment by producing plant alkaloids from the plants.

Nearly all plants that have been reviewed in this paper are commonly edible vegetables, fruits, as well as herbs. However, in this review, certain parts of the plants, such as leaves and flowers that are not commonly consumed and also proven to have anti-cancer effects against CRC were also included to reveal the amazing facts that local natural product own to the communities. For instance, *Abelmoschus esculentus* (okra) plants are usually planted for their fruits which are included in various Malaysian dishes.

However, Deng *et al*., (2020) reported that Okra flower extract inhibited CRC proliferation with a cytotoxic effect (21). Moreover, besides the fruits of the Psidium guajava (jambu batu) plant (22), their leaves were also explored to interrupt the CRC viability (23,24). In addition, *Moringa oleife* as a natural gift from the vegetable family has been widely investigated for wound healing, antidiabetic, antiulcer, antihypertensive, antioxidant, and anti-cancer properties with all parts of the plant; stem, leaves, and bark (12,25).

In Malaysia, pineapple agriculture comes in different varieties; Morris, Sarawak, Josapine, MD2, and N36 play a vital role in the economic sector and are Malaysia's favorite fruit. Usually, the stem, skin, and core part of this fruit will be removed, and only the soft flesh will be served since the stem, skin, and core have a fibrous and hard texture (26). However, little do we know that the core and stem of pineapple fruit are reported to have high fiber content that keeps the gastrointestinal tract healthy (27). It is known that colorectal cancer could arise from abnormal cell proliferation and inflammation in the intestinal lining (28). Bromelain in pineapple fruits is highly explored for its anti-inflammatory and apoptotic properties because intestinal lines can absorb the intact form of bromelain (29). This proteolytic enzyme carries out the anti-proliferation activity by deactivating the AKT and ERK cell survival components and stimulating p53 expression to activate the cell death cascade (27,28,30,31). Furthermore, bromelain is also known for deactivating blood clots; this way, it was stated to prevent inflammation in the intestine (30). Therefore, one could potentially prevent colorectal cancer in the very initial stage by consuming this tropical fruit, as bromelain has the potential to cure inflammations and kills abnormal cells in the intestines.

Potential Management for Chemotherapy-Induced Adverse Effects

Undeniably, throughout the world, clinical cancer treatments are still very much dependent on commercial chemotherapeutic drugs such as oxaliplatin and cisplatin, which causes a plethora of adverse effects on other healthy organs in the body such as the skin, liver, kidney, and intestine (32). The most common side effects of colorectal cancers are nausea, vomiting, mucositis, and diarrhea (33). Even though all of these chemotherapy toxicities are mostly treatable with the current medications, relying entirely on commercial drugs multiplies the treatment cost spent by patients (34,35). In addition, chemotherapy and radiotherapy anti-cancer treatment suppresses the immune system and reduces the serum level that contains antioxidant compounds in patients who suffer delayed recovery from the side effects (36). Hence, besides the anti-cancer properties, most of the plants mentioned in Table 1 also have the potential to be utilized in treating the side effects of chemotherapy in colorectal cancer as equally as turmeric and ginger plants which were proven to heal the side effects of chemotherapy-induced neurotoxicity, nausea, and vomiting (33).

Diarrhea

After tumor resections or chemotherapy treatment, immunosuppressed patients experience diarrhea due to damage to the intestinal tissue lining or due to secretions of enterotoxin from pathogens (31). Interestingly pineapple consumption before surgery was stated to relieve the post-surgery and post-chemotherapy effects. Bromelain in the pineapple has been found to prevent the secretions of enterotoxin from infected pathogens that cause diarrhea. Simultaneously, in the intestine, bromelain was reported to interact with adenosine 3' : 5'-cyclic monophosphatase, guanosine 3' : 5'-cyclic monophosphatase, and calcium-dependent signaling cascades of secretory signaling pathways to relief diarrhea effects (29). Next, in *Moringa oleifera* (37), *Psidium guajava* (38), *Cymbopogon citratus* (39,40), *Piper betle* (41), *Catharanthus roseus* (42,43), *Solanum melongena L.* (44), *Vigna unguiculata (L.) Walp.*(45), *Camellia Sinensis* (46,47), *Mesua ferrea L.* (48), and *Parkia speciosa* (49) extracts, phenolic compounds such as Tannins, Saponins, and Flavonoids antidiarrheal properties by preventing the growth of bacteria in the intestinal lining. Tannins interrupt bacteria formation by deactivating the DNA topoisomerase by producing a film to shield the intestine from absorbing toxins released by pathogens. At the same time, saponins and flavonoids can prevent diarrhea by breaking down the bacterial cell membrane, controlling the spasmolytic effect (50), and interrupting the cytochrome C in the energy metabolism process (37,51,52). The abundance of quercetin in *Psidium guajava* was reported to increase calcium absorption by controlling the peristaltic activity of the intestine (38,53). *Momordica Charantia L.* (54) *and Senna alata* (55,56) were also stated to have antidiarrheal properties. However, the mechanism involved in the process was not thoroughly discussed.

Mucositis

Oral and intestinal mucositis are the two main mucositis that arises from damage caused by chemotherapeutic drugs or radiation on normal tissues (33). Eventually, this damage could lead to bacterial infections causing immunosuppressed patients who underwent anti-cancer treatment to suffer more. Oral mucositis can be found around the mouth, such as on the tongue, the floor under the tongue, or on the inner lining of the cheeks. At the same time, intestinal mucositis is found in the intestinal lining. Damage caused in the salivary glands in the mouth and secretory cells in the intestine leading to mouth dryness and failure in bowel movement lubrication could also cause mucositis. Once patients are introduced to these toxic agents, the body system immediately produces ROS by activating the nuclear factor-kB (NF-kB) signaling transduction cascade, which promotes pro-inflammatory cytokines secretions.

Table 1: Anti-cancer effects of Locally Available Plants Against Colorectal Cancer

Plant	Common name	Parts	Compound	Properties	Study	Mechanism	References
Moringa oleifera	"Pokok kelor / merunggai"	Leaves Bark	D-allose Eugenol (phenolic compound)	Antioxidant	*In-vitro* -HCT-8	-Induces apoptosis -Inhibits cell proliferation by targeting E2F family	(12)
Psidium guajava	"Jambu batu"/ Guava	Leaves	NM	Antioxidant	*In-vitro* -HCT116	Inhibited CRC cell viability	(23)
		Fruits	Gallic acid, Gallocatechin, Procyanidin B, Guavinoside B	Antiproliferative	*In-vitro* -HT-29	Inhibited CRC cell proliferation	(22,83)
Citrullus lanatus	"Tembikai"/ Watermelon	Fruits	L-citrulline	Antiproliferative	*In-vivo* Rats	Rats had lowered proliferation index in the colon.	(84)
Ananas comosus	"Nenas"/ Pineapple	Fruits Stem	Bromelain	Anticarcinogenic/ Antiinflammatory	*In-vitro* -HT-29 HSF1184	-Selectively suppress colon cells without harming normal cells	(27,31)
Pachyrhizus tuberosus	"Sengkuang"/Yam bean	Tuber	Rotenoids, Rotenone, Isoflavanone	Anticancer	*In-vitro* -HCT116	-Cytotoxic effect against CRC cell lines	(85)
Solanum melongena L.	"Terung"/Eggplant	Fruit	Delphinidin, Nasunin	Antioxidant	*In-vitro* -HT-29 -HCT116	-Promoted GCR expression in CRC cells -Reduced DNA damage	(86)
Cymbopogon citratus	"Serai"/ lemongrass	Leaves	NM	Anticancer	*In-vitro* NCM-460 -HCT116 -HT-29	-Selectively induces apoptosis in CRC -Inhibited growth of human CRC	(87)

					In-vivo -Immunocompromised mice	xenograft in mice with orally administration of lemon grass extract -Reduces chemotherapy side effects	
Piper betle	"Sirih"	Leaves	Hydroxychavicol	Antiproliferative	*In-vitro* -HT-29	G0/G1 phase cell cycle arrest Increased cell death	(88,89)
Catharanthus roseus	"Kemuning cina"	NM	Catharanthine	Anticancer	*In-vitro* -HCT-112	-Cytotoxic against HCT-112 cell line	(90)
		Stem	Saponins, phenolics	Anticancer	*In-vitro* -HT-29	-Inhibits CRC cell growth	(91)
Abelmoschus esculentus	"Bendi"/Okra	Flowers	Flavonoids	Antioxidant	*In-vitro* HCT116, DLD-1, NCM460 *In-vivo* Mice CT26 xenograft	-Cytotoxic effect against CRC cell lines -Suppressed tumor proliferation	(21)
Momordica Charantia L.	"Peria"/Bitter melon	Fruits	Flavonoids	Anticancer	*In-vitro* WiDr	-Inhibited cell growth	(92)
		Fruits	Flavonoids	Anticancer	*In-vitro* SW480 and HT-29	-S and G2/M phase cell cycle arrest -Induce autophagy	(93)
Oenanthe javanica	"Selom"	Leaves	Chlorophyll, β-carotene, Vit E, Vit C, Se, Zn	Antigenotoxic	*In-vitro* HCT116	Inhibited H_2O_2-induced DNA damage	(94)
Psophocarpus tetragonolobus	"Kacang botol"/winged beans	Fruits	NM	Antiproliferative	*In-vitro* HT-29	-Inhibits CRC cell growth	(95)
Parkia speciosa	"Petai"	Seeds, Pods	Phenolic acids, flavonoids, and	Antioxidant	*In-vitro* HCT116	-Improved radical scavenging	(96)

			tannins			activity	
Houttuynia cordata	"Pokok hanyir ikan"/ chameleon plant	Leaves	NM	Anticancer	*In-vitro* -HT-29	-Enhanced reactive oxygen species (ROS) production -Induced mitochondrial-dependent apoptosis.	(97)
Senna alata	"Gelenggang"	Leaves	Flavanoids-Quercetin, kaempferol, Luteolin Phenolic acid - Caffeic acid	Anticancer	*In-vitro* HT-29 and HCT 116	Cytotoxic effect against CRC cell lines	(98)
Mentha spicata	"Daun pudina"/Spearmint	Leaves	Piperitenone oxide	Anticarcinogenic	*In -vitro* RCM-1	Induced differentiation effects	(99)
Euphoria longana Lam	"Longan"	Dried seeds	Corilagin, gallic acid, ellagic acid	Anti-angiogenesis	*In-vitro* SW480	Reduced VEGF expression and secretion.	(100)
		Flowers	NM	Anticancer	*In-vitro* SW480 and Colo 320DM	Inhibit proliferation Cell cycle arrest in the S phase	(101)
Annona squamosa linn	"Pokok Nona"	Leaves	Sesquiterpenes	Antioxidant	*In-vitro* HCT116	Cytotoxic, antimigration, and induced apoptosis in CRC cells	(102)
		Seeds	Acetogenins	Antiproliferative	*In-vitro* HT-29	Inhibit the proliferation of CRC	(103)
Vigna unguiculata (L.) Walp.	"Kacang mata hitam"/cowpeas	Seeds	Amino acids, organic acids, sugar, choline, uracil	Anticancer	E705, DiFi, SW480 and Caco-2	-Reduced phosphorylated EGFR activity	(104)
Nypa fruticans	"Nipah"	Leaves	Polyisoprenoids	Chemotherapeutic	*In-vitro*	-Upregulated p53	(105)

(Wurmb)	Nipah palm			effect	WiDr	gene expression and downregulated EGFR, PI3K, AKT1, and mTOR gene expressions. -Inhibited WiDr growth.	
Camellia sinensis	"Pokok teh"/Tea plant	Leaves	NM	Anticancer	*In-vitro* Caco-2 L929	Selective cytotoxic effect against CRC	(106)
Mesua ferrea	"Penaga lilin"	Stem Bark	α-amyrin Betulinic acid contents	Anticancer	*In-vitro* HCT-116	-Induce apoptosis by upregulating caspases-9 and -3/7, p53, Myc/Max, and TGF-β signaling pathways	(107)

"Local name in the Malay language" *NM: Not mentioned, CRC: Colorectal cancer *Vit: vitamin

These pro-inflammatory cytokines, such as TNF-a, IL-1b, and IL-6 secretions, reactivate the MAPK cascade, and the combination of all the above processes induces the mucosal lesion (57). Remarkably, Mentha spicata extracts exhibited reduced IL-1β cytokines and intestine histological improvement in irinotecan-induced mucositis rats (58). *Houttuynia cordata* was reported to enhance the oral immune response by controlling the β-defensin 2, IL-8, and CCL20 expression signaling pathways (59). The compounds in *Momordica Charantia L*. (60) and *Moringa oleifera* extracts have proven their anti-inflammatory and anti-microbial properties by alleviating NF-kB signaling cascades in CRC patients (12) and inhibiting oral pathogen that causes mucositis, respectively (61). Likewise, flavonoids such as Terpinenes in *Psidium guajava* are known as bacteriostatic agents due to their ability to break down the cell membrane and inhibit bacterial growth (38,62).

Moreover, evidence stated that polyphenol in *Ananas comosus* speeds up the oral ulcer healing time by stimulating the fibroblast cell proliferation (57). Next, the *Piper betle* extract has effective antiulcerogenic properties where it protects the ulcer area by inducing mucus production, reducing damaged proteins, and increasing the free radicals scavenging process (63). The antioxidant content in the decoction carries out cellular protection from chemotherapy-induced free radicals; ROS neutralizes the free radical by donating electrons to the free radicals (36). *Psophocarpus tetragonolobus* (64) *and Nypa fruticans (Wurmb)* (65) also found antiulcer properties. However, the mechanism involved in the process was not thoroughly discussed. Therefore, this plant can be potentially used to treat mucositis caused by chemotherapy treatments due to its antiulcer and anti-inflammation properties. Moreover, vincamine and vindoline alkaloids found in *Catharanthus roseus* and *Abelmoschus esculentus* were proven for gastroprotective activity, which was found to have therapeutic antiulcer properties against gastric-damaged rats (42,66).

Nausea and Vomit

According to Grunberg and Slusher (2013), administering an anti-cancer drug such as cisplatin accumulates toxins in the body. These toxins impair the intestinal lining. Subsequently, serotonin is secreted by enterochromaffin cells in the gastrointestinal (GI) tract. The secreted serotonins directly attach to the 5-hydroxytryptamine-3 (5-HT3) receptors. 5-HT3 receptors are found in vagal afferents that connect impulses from the GI tract to the brain. Meanwhile, another pathway collectively participates in nausea and vomiting effects, activating the chemoreceptors zone that holds area postrema. Toxins in the blood can be directly detected by the area postrema by secretions of serotonin, dopamine, and substance P (SP) (67). Intriguingly, *Moringa oleifera* (68) and *Piper betle* (69) were proven to control the neurotransmitter serotonin and dopamine-receptor interactions to stop nausea and vomiting (68). In addition, Rajabalizadeh *et al*., (2022) reported that *Mentha spicata* regulates nausea and vomiting sensations by mediating 5-HT antagonists (70). The antioxidant compound of *Psidium guajava, Cymbopogon citratus* (40)*, Camellia Sinensis* (46,47), and *Ananas comosus* were also stated to relieve the vomiting and nausea sensation (71–73). However, the mechanism involved in the process was not thoroughly discussed.

Traditional Ways of Natural Products Consumptions

The preparation and administration of natural products depend on the disease or condition treated. Traditionally, most Malaysian plants with medicinal properties are consumed raw, dried in form, or cooked as one of the ingredients in the main dish. Some also consume broth made from boiled natural products. Similarly, *pudina* leaves, petai, okra flowers, and *selom* leaves are primarily included in salads and rice garnishing. *Kemuning cina* stems, guava leaves, chameleon plant leaves, *gelenggang* leaves, lemongrass leaves, okra leaves, merunggai leaves, and *pokok nona* leaves can be used to make broth and consumed when it is warm (74–76). In addition, merunggai leaves that have been dried and powdered can also be consumed by mixing them in hot water. Lemongrass is also one of the widely used ingredients in Malay dishes and is commercially sold as tea. Most of the dried forms of leaves and seeds from the natural products listed on the tables can be made into tea. Fruits like guava, pineapple, longan, and watermelon are peeled or sliced and consumed raw. Watermelon seeds are usually roasted before consumption. For best results, bitter melon is blended, and the fresh juice is consumed as needed in a small portion (77). Therefore, Malaysians have a handful of valuable natural product sources that can be included in their daily meals to prevent and treat CRC without depending on imported costly food.

Economic Prospect of Natural Products

All these natural products' health benefits reviewed can be used to encourage Malaysians to generate income through the agricultural activity as they are highly demanding tropical plants which could improve Malaysia's economy. Furthermore, research reported that more than 50% of the elderly in Malaysia 83 and also from other countries 84,85 prefer herbal and dietary supplements over conventional medications to maintain good health (78). This statement demonstrates that Malaysians and others have good perceptions and knowledge of the worth of natural products, which indirectly exhibits the purchasing power of natural products.

The emergence of Sustainable Natural Products in Today's Era

Apart from tropical natural products grown on land, Malaysia is also rich in algal sources. Recent research on algae, especially microalgae, has given great insights into the medicinal properties that could be used as biofuel and to treat various diseases. This is because microalgae cultivation requires no land space, and it is the fastest growing organism (79) that is concomitantly known to reduce the carbon dioxide emission in the environment as it absorbs a high amount of carbon dioxide to grow (80). Microalgae such as *Arthrospira* (Spirulina), *Chaetoceros, Chlorella*, *Dunaliella,* and *Isochrysis* are widely commercialized in Malaysia's agricultural industry (81). The enormous health benefits of *Spirulina sp.* have urged scientists and industrial professionals to expand their research into searching for other microalgae that might have similar or enhanced properties to *Spirulina* sp., leading to the discovery of *Tetraselmis* sp. *Tetraselmis suecica* has recently become a highly explored microalgae due to its lipid accumulation that potentially has anti-cancer properties(82). Therefore, income generation from this agriculture exceptionally high potential to improve economic prospects if Malaysians understand these plants' valuable properties and microalgal research for better living.

Limitations

Most of the investigations that showed local plants have anti-cancer properties against CRC and the ability to facilitate chemotherapy-induced side effects were *in-vitro* studies. Very little has been done *in-vivo in* Malaysia. The cell lines used in the research vastly influence the results because HCT-8, HT-29, HCT-116, DLD-1, WiDr, SW480, Colo 320DM, and Caco-2 vary in the origin, metabolic mechanism, and mutations of the cell lines. Therefore, preliminary results in the *in-vitro* studies supported by *in-vivo* studies make it challenging to agree on proving the plants' effectiveness against CRC. This shows that the prospect of research focusing on locally available plants still has much more to be explored for CRC treatment. Hence, this review urges researchers to delve further into the medicinal properties of the locally available plants against CRC to encourage Malaysian to lead a healthy lifestyle by having affordable and easily accessible healthy foods.

Conclusion

In conclusion, the locally available natural products have excellent medicinal properties against colorectal cancer. They have anti-inflammatory, antigenotoxic, antioxidant, anti-angiogenesis, and chemotherapeutic agent properties that Malaysians can include in their daily diet to prevent colorectal cancer. Moreover, these natural products can also be utilized to treat post-cancerous complications. Low-income families can grow these plants to lead a healthy lifestyle with low-cost natural products and possibly generate income, as not all listed plants can grow in various climate conditions unless in Malaysia, which raises the demand for these plants. Therefore, this review urges local academia to conduct more research on local natural products in treating diseases as this could help improve the well-being of low-income communities in Malaysia.

Competing interests

The authors declare that they have no conflicts of interest.

Consent

Not applicable.

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References

1. Li J, Zhou L, Liu Y, Yang L, Jiang D, Li K, et al. Comprehensive Analysis of Cyclin Family Gene Expression in Colon Cancer. Front Oncol. 2021;11.
2. Gururuloo SL, Sandai DA, Salleh MSM, Abduraman MA, Shahpudin SNM. Aberrant G1 / S Phase Cyclins in Human Cancer Tissues. Mal J Heal Sci. 2021;17(SUPP9):142–7.
3. Benarba B, Pandiella A. Colorectal cancer and medicinal plants: Principle findings from recent studies. Biomed Pharmacother. 2018 Nov 1;107:408–23.
4. Zeestraten ECM, Maak M, Shibayama M, Schuster T, Nitsche U, Matsushima T, et al. Specific activity of cyclin-dependent kinase i is a new potential predictor of tumour recurrence in stage II colon cancer. Br J Cancer. 2012;106(1):133–40.
5. Ibrahim NRW, Chan HK, Soelar SA, Azmi AN, Said RM, Hassan MRA. Incidence, clinico-demographic profiles and survival rates of colorectal cancer in Northern Malaysia: Comparing patients above and below 50 years of age. Asian Pacific J Cancer Prev. 2020;21(4):1057–61.
6. Chandran A, Mustapha FI, Tamin NSI, Hassan MRA. Overview of colorectal cancer screening programme in Malaysia. Med J Malaysia. 2020;75(3):235–9.
7. Murphy N, Moreno V, Hughes DJ, Vodicka L, Vodicka P, Aglago EK, et al. Lifestyle and dietary environmental factors in colorectal cancer susceptibility. Vol. 69, Molecular Aspects of Medicine. Elsevier Ltd; 2019: 2–9.
8. Gearhart S, Ahuja N. Early Diagnosis and Treatment of Cancer Series: Colorectal Cancer. Elsevier Heal Sci. 2011;

9. Aiello P, Sharghi M, Mansourkhani SM, Ardekan AP, Jouybari L, Daraei N, et al. Medicinal plants in the prevention and treatment of colon cancer. Oxid Med Cell Longev. 2019;2019.
10. Sawicki T, Ruszkowska M, Danielewicz A, Niedźwiedzka E, Arłukowicz T, Przybyłowicz KE. A review of colorectal cancer in terms of epidemiology, risk factors, development, symptoms and diagnosis. Vol. 13, Cancers. MDPI AG; 2021
11. Ghee LK. A Review of Colorectal Cancer Research in Malaysia. Med J Malaysia. 2014;69(8):23–32.
12. Al-Asmari AK, Albalawi SM, Athar MT, Khan AQ, Al-Shahrani H, Islam M. Moringa oleifera as an anti-cancer agent against breast and colorectal cancer cell lines. PLoS One. 2015;10(8).
13. Desai A, Qazi G, Ganju R, El-Tamer M, Singh J, Saxena A, et al. Medicinal Plants and Cancer Chemoprevention. Curr Drug Metab. 2008;9(7):581–91.
14. Zhao L, Shanks J V. Metabolic profiling of terpenoid indole alkaloids in transgenic catharanthus roseus hairy roots. Food, Pharm Bioeng Div 2013 - Core Program Area 2013 AIChE Annu Meet Glob Challenges Eng a Sustain Futur. 2013;(April):434.
15. Hacker M. Adverse Drug Reactions. Pharmacology. 2009;327–52.
16. Ojima I, Lichtenthal B, Lee S, Wang C, Wang X. Taxane anticancer agents: A patent perspective. Vol. 26, Expert Opinion on Therapeutic Patents. 2016. p. 1–20.
17. Li F, Jiang T, Li Q, Ling X. Camptothecin (CPT) and its derivatives are known to target topoisomerase I (Top1) as their mechanism of action: Did we miss something in CPT analogue molecular targets for treating human disease such as cancer?. Vol. 7, American Journal of Cancer Research. 2017. p. 2350–94.
18. Department of Statistics Malaysia Official Portal. [cited 2022 Sep 15]. Available from: https://www.dosm.gov.my/v1/index.php?r=column/cthemeByCat&cat=493&bul_id=VTNHRkdiZkFzenBNd1Y1dmg2UUlrZz09&menu_id=amVoWU54UTl0a21NWmdhMjFMMWcyZz09
19. Hashim YZH-Y, Gill CIR, Latimer C, Ternan N, Abbas P. Studies of Malaysian Plants in Prevention and Treatment of Colorectal Cancer. Color Cancer - From Pathog to Treat. 2016.
20. Macharia JM, Mwangi RW, Rozmann N, Wagara IN, Kaposztas Z, Varjas T, et al. A systematic review of selected plants and their metabolites with anticolorectal cancer effects. Phytomedicine Plus [Internet]. 2022;2(4):100332.
21. Deng Y, Li S, Wang M, Chen X, Tian L, Wang L, et al. Flavonoid-rich extracts from okra flowers exert antitumor activity in colorectal cancer through induction of mitochondrial dysfunction-associated apoptosis, senescence and autophagy. Food Funct. 2020 Dec 1;11(12):10448–66.
22. Blancas-Benitez FJ, Pérez-Jiménez J, Sañudo-Barajas JA, Rocha-Guzmán NE, González-Aguilar GA, Tovar J, et al. Indigestible fraction of guava fruit: Phenolic profile, colonic fermentation and effect on HT-29 cells. Food Biosci. 2022.
23. Lok B, Abdul Majid A, Baharetha HM, Asif M. In vitro and ex vivo anticolorectal cancer effects of ethanolic *Psidium guajava* (Guava) leaf extract through inhibition of angiogenesis and colony formation. Front Pharmacol. 2018;9.
24. Lok B, Sandai D, Baharetha HM, Nazari VM, Asif M, Tan CS, et al. Anticancer effect of *Psidium guajava* (Guava) leaf extracts against colorectal cancer through inhibition of angiogenesis. Asian Pac J Trop Biomed. 2020;10(7):293–307.
25. Stohs SJ, Hartman MJ. Review of the Safety and Efficacy of *Moringa oleifera*. Phyther Res [Internet]. 2015 Jun 1 [cited 2022 Apr 29];29(6):796–804.
26. Mohd Ali M, Hashim N, Abd Aziz S, Lasekan O. Pineapple (*Ananas comosus*): A comprehensive review of nutritional values, volatile compounds, health benefits, and potential food products. Vol. 137, Food Research International. Elsevier Ltd; 2020. p. 109675.
27. Gani MBA, Nasiri R, Almaki JH, Majid FAA, Marvibaigi M, Amini N, et al. In Vitro Antiproliferative Activity of Fresh Pineapple Juices on Ovarian and Colon Cancer Cell Lines. Int J Pept Res Ther. 2015;21(3):353–64.
28. Kargutkar S, Brijesh S. Anti-inflammatory evaluation and characterization of leaf extract of *Ananas comosus*. Inflammopharmacology. 2018;26(2):469–77.
29. Pavan R, Jain S, Shraddha, Kumar A. Properties and Therapeutic Application of Bromelain: A Review. Biotechnol Res Int. 2012:1–6.
30. Chang T-C, Wei P-LI, Takondwa Makondi P, Chen W-T, Huang C-Y, ChangID Y-J. Bromelain inhibits the ability of colorectal cancer cells to proliferate via activation of ROS production and autophagy. 2019.
31. Romano B, Fasolino I, Pagano E, Capasso R, Pace S, De Rosa G, et al. The chemopreventive action of bromelain, from pineapple stem (*Ananas comosus L.*), on colon carcinogenesis is related to antiproliferative and proapoptotic effects. Mol Nutr Food Res. 2014;58(3):457–65.
32. Nurgali K, Jagoe RT, Abalo R. Editorial: Adverse Effects of Cancer Chemotherapy: Anything New to Improve Tolerance and Reduce Sequelae? Front Pharmacol. 2018;9:245.
33. Chen D, Zhao J, Cong W. Chinese Herbal Medicines Facilitate the Control of Chemotherapy-Induced Side Effects in Colorectal Cancer: Progress and Perspective. Front Pharmacol. 2018;9:1442.
34. Miroddi M, Sterrantino C, Simonelli I, Ciminata G, Phillips RS, Calapai G. Risk of grade 3-4 diarrhea and

mucositis in colorectal cancer patients receiving anti-EGFR monoclonal antibodies regimens: A meta-analysis of 18 randomized controlled clinical trials. Crit Rev Oncol Hematol. 2014;96(2):355–71.
35. Miknevicius P, Zulpaite R, Leber B, Strupas K, Stiegler P, Schemmer P. Molecular Sciences The Impact of Probiotics on Intestinal Mucositis during Chemotherapy for Colorectal Cancer: A Comprehensive Review of Animal Studies. 2021.
36. Singh K, Bhori M, Kasu YA, Bhat G, Marar T. Antioxidants as precision weapons in war against cancer chemotherapy induced toxicity – Exploring the armoury of obscurity. Saudi Pharm J [Internet]. 2018;26(2):177–90.
37. Isitua CC, Ibeh IN, Olayinka JN. Antibacterial Activity of *Moringa Oleifera Lam* Leaves on Enteric Human Pathogens. INDIAN J Appl Res. 2016;6(8):553–7.
38. Naseer S, Hussain S, Naeem N, Pervaiz M, Rahman M. The phytochemistry and medicinal value of *Psidium guajava (*guava). Clin Phytoscience. 2018;4(1).
39. Yaqeen Z, Naqvi N-H, Fatima N, Imran H, Sohail T, Atiq-ur-Rahman Z-R, et al. Evaluation of anti-emetic activity of *Cymbopogon citratus* (DC.) Stapf. Int J Biol Biotechnol. 2011;8(3):419–22.
40. Marchaoui M, Kthiri Z, Jabeur MB, Hamada W. Ethnobotanical and phytopharmacological notes on Cakile maritima. Phytotherapie. 2018;16(S1):S197–202.
41. Sundang M, Nasir SNS, Sipaut CS, Othman H. Antioxidant Activity, Phenolic, Flavonoid and Tannin Content of *Piper Betle* and *Leucosyke Capitella Murni*. Malaysian J Fundam Appl Sci. 2012;8(1):1–6.
42. Renjini KR, Gopakumar G, Latha MS. Medicinal Properties of Phytochemicals in Catharanthus Roseus-A Review. 2018.
43. Aslam MS, Ahmad MS, Ahmad MA, Akhlaq M. An updated review on phytochemical and pharmacological propeties of *piper sarmentosum.* Curr Trends Biotechnol Pharm. 2017;11(4):345–56.
44. Mbah U, Egbuonu A. Ethanolic Extract of *Solanum melongena Linn* Fruit Mitigated Monosodium Glutamate-Induced Oxidative Stress. Int J Biochem Res Rev. 2017;18(2):1–8.
45. Alfa AA, Tijani KB, Omotoso OD, Junaidu Y, Sezor AA. Nutritional Values and Medicinal Health Aspects of Brown, Brown-Black and White Cowpea (*Vigna unguiculata L. Walp*.) Grown in Okene, Kogi State, Nigeria. Asian J Adv Res Reports. 2020;(December):114–24.
46. Tewari I, Sharma L, Gupta GL. Synergistic antioxidant activity of three medicinal plants *Hypericum perforatum*, *Bacopa monnieri*, and *Camellia sinensis*. Indo Am J Pharm Res. 2014;4(5):2563–8.
47. Namita P, Mukesh R, Vijay KJ. *Camellia sinensis* (green tea): A review. Glob J Pharmacol. 2012;6(2):52–9.
48. Puspitarini PM., Pratama I., Suryadi B. Anti-Diarrheal Activity of Aqueous Extract of Nagasari Flowers (*Mesua ferrea L.*) in Balb/c Mice Induced by Escherichia coli. J Farm Sains dan Komunitas [Internet]. 2019;3(2):58–66.
49. Saleh MSM, Jalil J, Zainalabidin S, Asmadi AY, Mustafa H, Kamisah Y. Molecular Sciences Genus Parkia: Phytochemical, Medicinal Uses, and Pharmacological Properties. 2021.
50. Chaudhary N, Tripathi S. A Review on Multipurpose Plant: *Psidium Guajava.* Int J Pharmacogn Phytochem Res. 2014;6(1):118–21.
51. Misra A, Srivastava S, Srivastava M, Sharad Srivastava C. Evaluation of anti diarrheal potential of *Moringa oleifera (Lam*.) leaves. J Pharmacogn Phytochem. 2014;2(5):43–6.
52. Adji AS, Atika N, Kusbijantoro YB, Billah A, Putri A, Handajani F. A review of Leaves and Seeds *Moringa oleifera* Extract: The potential *Moringa oleifera* as Antibacterial, Anti-Inflammatory, Antidiarrhoeal, And Antiulcer Approaches To Bacterial Gastroenteritis. Open Access Maced J Med Sci. 2022;10(F):305–13.
53. Rattanachaikunsopon P, Phumkhachorn P. Contents from leaves of Psidium guajava. J Med Plants Res. 2010;4(5):393–6.
54. Sharma S, Gautam A, Bhadauria R, Gupta M, Gautam AK. *Momordica charantia linn.* (Karela): Nature's silent healer. Artic Int J Pharm Sci Rev Res. 2011
55. Oladeji OS, Adelowo FE, Oluyori AP, Bankole DT. Ethnobotanical Description and Biological Activities of *Senna alata.* Evidence-based Complement Altern Med. 2020.
56. El-Mahmood, Doughari. Phytochemical screening and antibacterial evaluation of the leaf and root extracts of *Cassia alata Linn*. African J Pharm Pharmacol. 2008;2(7):124–9.
57. Chang HP, Huang MC, Lei YP, Chuang YJ, Wang CW, Sheen LY. Phytochemical-rich vegetable and fruit juice alleviates oral mucositis during concurrent chemoradiotherapy in patients with locally advanced head and neck cancer. J Tradit Complement Med. 2022;12(5):488–98.
58. Abdul Jabbar AAS, Kathem SH. The protective effect of *Mentha spicata* ethanolic extract on irinotecan-induced mucositis in mice. Iraqi J Pharm Sci. 2019;28(1):37–43.
59. Rafiq S, Hao H, Ijaz M, Raza A. Pharmacological Effects of *Houttuynia cordata Thunb* (*H. cordata*): A Comprehensive Review. Pharmaceuticals. 2022;15(9):1079.
60. Ji S, Zhang Q. Momordica charantia polysaccharides alleviate diarrhea-predominant irritable bowel syndrome by regulating intestinal inflammation and barrier via NF-kB pathway. Allergol Immunopathol

(Madr). 2022;50(3):62–70.
61. Patel P. *Moringa Oleifera*-Nature's Gold. Imp J Interdiscip Res. 2017;3(5).
62. Agbor AM, Naidoo S. Plants Used by African Traditional Healers in the Management of Oral Diseases: A Review. Int J Res -Granthaalayah. 2019;7(8):273–86.
63. Biswas P, Anand U, Saha SC, Kant N, Mishra T, Masih H, et al. Betelvine (*Piper betle L.*): A comprehensive insight into its ethnopharmacology, phytochemistry, and pharmacological, biomedical and therapeutic attributes. Vol. 26, Journal of Cellular and Molecular Medicine. John Wiley & Sons, Ltd; 2022. p. 3083–119.
64. Rajan D. A Review on Pharmacognostical, Phytochemical and Pharmacological aspects of *Psophocarpus tetragonalobus* . Res J Pharmacogn Phytochem. 2018;10(4):331.
65. Nugroho GDWI, Wiraatmaja MF, Pramadaningtyas PS, Febriyanti S, Liza NOR, Naim D. Review : Phytochemical composition, medicinal uses and other utilization of *Nypa fruticans*. Bonorowo Wetl. 2021;10(1):51–65.
66. Ortaç D, Cemek M, Karaca T, Büyükokuroğlu ME, Özdemir Z, Kocaman AT, et al. In vivo anti-ulcerogenic effect of okra (*Abelmoschus esculentus*) on ethanol-induced acute gastric mucosal lesions. Pharm Biol. 2018;56(1):165–75.
67. Grunberg SM, Slusher B. Clinical Roundtable Monograph Emerging Treatments in Chemotherapy-Induced Nausea and Vomiting Moderator. Clin Adv Hematol Oncol. 2013;11(2):3–8.
68. Upadhye KP, Rangari VD, Mathur VB. Antimigraine activity study of *Moringa oleifera* leaf juice. Int J Green Pharm. 2012;6(3):204–7.
69. Bhardwaj K, Devi A, Mishra R, Rana S. A Review on Anti-Inflammatory Potential of *Piper betle.* World J Pharm Med Res [Internet]. 2022;8(2):83–90. A
70. Rajabalizadeh R, Ghasemzadeh Rahbardar M, Hosseinzadeh H. Medicinal herbs in treating chemotherapy-induced nausea and vomiting: A review. Phyther Res. 2022.
71. Mittal P, Gupta V. Phytochemistry and pharmacological activities of *psidium guajava*: a review. Int J Phar Sci Res. 2010;1(9):9–19.
72. Farid Hossain M, Akhtar S, Anwar M. Nutritional Value and Medicinal Benefits of Pineapple. Int J Nutr Food Sci. 2015;4(1):84–8.
73. Jo WS, Choi YJ, Kim HJ, Nam BH, Hong SH, Lee GA, et al. Anti-inflammatory Effect of Microalgal Extracts from Tetraselmis suecica. Food Sci Biotechnol. 2010;19(6):1519–28.
74. Daun Gelenggang (*Cassia Senna*) - PORTAL MyHEALTH. [cited 2022 Sep 15].
75. Daun Amis-Amisan *(Houttuynia Cordata*) Paramita Foundation Riau - Ayo Beramal Melalui Paramita Foundatio. [cited 2022 Sep 15]. Available from: https://www.paramitafoundationriau.com/tanaman-herbal/detail/6/6-daun-amisamisan-houttuynia-cordata
76. Serai Wangi - Jabatan Perhutanan Semenanjung Malaysia. [cited 2022 Sep 15]. Available from: https://www.forestry.gov.my/my/slideshow/97-herba/315-serai-wangi
77. Demayo CG, Olowa L. Pages: 204-215 To Cite This Article: Lilybeth Olowa and Cesar G. Demayo., Ethnobotanical Uses of Medicinal Plants among the Muslim Maranaos in Iligan City. Vol. 9, Advances in Environmental Biology. 2015.
78. Wahab MSA, Zaini MH, Ali AA, Sahudin S, Mehat MZ, Hamid HA, et al. The use of herbal and dietary supplement among community-dwelling elderly in a suburban town of Malaysia. BMC Complement Med Ther. 2021;21(1):1–13.
79. Sarbatly R, Suali E. Potential use of carbon dioxide by microalgae in Malaysia. Int J Glob Environ Issues. 2012;12(2–4):150–60.
80. Abd El-Hack ME, Abdelnour S, Alagawany M, Abdo M, Sakr MA, Khafaga AF, et al. Microalgae in modern cancer therapy: Current knowledge. Biomed Pharmacother. 2019;111:42–50.
81. Rajkumar R, Sobri Takriff M. Prospects of Algae and their Environmental Applications in Malaysia: A Case Study. J Bioremediation Biodegrad. 2016;07(01):1–12.
82. Hussein HA, Mohamad H, Ghazaly MM, Laith AA, Abdullah MA. Cytotoxic effects of *Tetraselmis suecica* chloroform extracts with silver nanoparticle co-application on MCF-7, 4 T1, and Vero cell lines. J Appl Phycol 2019 321. 2019 Sep 13;32(1):127–43.
83. El Gizawy HA, El-Haddad AE, Attia YM, Fahim SA, Zafer MM, Saadeldeen AM. In Vitro Cytotoxic Activity and Phytochemical Characterization (UPLC/T-TOF-MS/MS) of the Watermelon *(Citrullus lanatus)* Rind Extract. Mol 2022, Vol 27, Page 2480. 2022;27(8):2480.
84. Fesseha M, Hong MY. Effects of Watermelon Consumption on Cellular Proliferation, and Apoptosis in Rat Colon (P05-019-19). Curr Dev Nutr. 2019;3.
85. Leuner O, Havlik J, Budesinsky M, Vrkoslav V, Chu J, Bradshaw TD, et al. Cytotoxic Constituents of *Pachyrhizus tuberosus* from Peruvian Amazon.
86. Jing P, Qian B, Zhao S, Qi X, Ye L, Mónica Giusti M, et al. Effect of glycosylation patterns of Chinese eggplant anthocyanins and other derivatives on antioxidant effectiveness in human colon cell lines. Vol. 172, Food Chemistry. Elsevier; 2015. p. 183–9.
87. Ruvinov I, Nguyen C, Scaria B, Vegh C, Zaitoon O, Baskaran K, et al. Lemongrass Extract Possesses Potent Anticancer Activity Against Human Colon Cancers, Inhibits Tumorigenesis, Enhances Efficacy of FOLFOX, and Reduces Its Adverse Effects. Integr

Cancer Ther. 2019;18.
88. Rajedadram A, Pin KY, Ling SK, Yan SW, Looi ML. Hydroxychavicol, a polyphenol from Piper betle leaf extract, induces cell cycle arrest and apoptosis in TP53-resistant HT-29 colon cancer cells. J Zhejiang Univ B. 2021;22(2):112–22.
89. Zamakshshari N, Ahmed IA, Nasharuddin MNA, Mohd Hashim N, Mustafa MR, Othman R, et al. Effect of extraction procedure on the yield and biological activities of hydroxychavicol from *Piper betle* L. leaves. J Appl Res Med Aromat Plants. 2021;24:100320.
90. Siddiqui MJ, Ismail Z, Aisha AFA, Abdul Majid AMS. Cytotoxic activity of *Catharanthus roseus* (Apocynaceae) crude extracts and pure compounds against human colorectal carcinoma cell line. Int J Pharmacol. 2010;6(1):43–7.
91. Pham HNT, Sakoff JA, Vuong Q Van, Bowyer MC, Scarlett CJ. Screening phytochemical content, antioxidant, antimicrobial and cytotoxic activities of *Catharanthus roseus (L.)* G. Don stem extract and its fractions. Biocatal Agric Biotechnol. 2018 Oct 1;16:405–11.
92. Yulianti E, Busman H, Nurcahyani N, Wahyuningsih S. Extract of Bitter Melon (*Momordica Charantia L*.) as a Cytotoxic and Anti Proliferaton Agent for Cells WiDr (Colon Cancer). Jl Prof Dr Soemantri Brojonegoro. 2021;(1).
93. Kwatra D, Subramaniam D, Ramamoorthy P, Standing D, Moran E, Velayutham R, et al. Methanolic extracts of bitter melon inhibit colon cancer stem cells by affecting energy homeostasis and autophagy. Evidence-based Complement Altern Med;2013.
94. Kwon D, Yoon S, Carter O, Bailey GS, Dashwood RH. Antioxidant and antigenotoxic activities of *Angelica keiskei*, *Oenanthe javanica* and *Brassica oleracea* in the Salmonella mutagenicity assay and in HCT116 human colon cancer cells. BioFactors. 2006;26(4):231–44.
95. Manosroi A, Akazawa H, Akihisa T, Jantrawut P, Kitdamrongtham W, Manosroi W, et al. In vitro anti-proliferative activity on colon cancer cell line (HT-29) of Thai medicinal plants selected from Thai/Lanna medicinal plant recipe database "MANOSROI III." J Ethnopharmacol. 2015 Feb 23;161:11–7.
96. Wong KL, Hoe Tan C, Shin Sim K, Jin Kim Y. Biological Activities of Supercritical Carbon Dioxide Extract of *Parkia speciosa* Seeds and Pods. Int J Bot. 2020;16(2):58–64.
97. Lai K, Chiu Y, Tang Y, Lin K, Chiang J. Houttuynia cordata Thunb Extract Inhibits Cell Growth and Induces Apoptosis in Human Primary Colorectal Cancer Cells. 2010;3556(91):3549–56.
98. Spriggs K, Onyegeme-Okerenta B, Bradshaw T. Ethyl Acetate Extract of *Senna alata (L) Roxb* Increases Cytotoxicity in the Human Breast, Prostate and Colorectal Cancer Cells. J Cancer Treat Res. 2018;6(3):44–53.
99. Nakamura Y, Hasegawa Y, Shirota K, Suetome N, Nakamura T, Chomnawang MT, et al. Differentiation-inducing effect of piperitenone oxide, a fragrant ingredient of spearmint (*Mentha spicata*), but not carvone and menthol, against human colon cancer cells. J Funct Foods. 2014;8(1):62–7.
100. Panyathep A, Chewonarin T, Taneyhill K, Surh YJ, Vinitketkumnuen U. Effects of dried longan seed (*Euphoria longana Lam*.) extract on VEGF secretion and expression in colon cancer cells and angiogenesis in human umbilical vein endothelial cells. J Funct Foods. 2013;5(3):1088–96.
101. Hsu CP, Lin YH, Zhou SP, Chung YC, Lin CC, Wang SC. Longan Flower Extract Inhibits the Growth of Colorectal Carcinoma. 2010;62(2):229–36.
102. Al-Nemari R, Al-Senaidy A, Semlali A, Ismael M, Badjah-Hadj-Ahmed AY, Ben Bacha A. GC-MS profiling and assessment of antioxidant, antibacterial, and anticancer properties of extracts of *Annona squamosa L.* leaves. BMC Complement Med Ther [Internet]. 2020 Oct 6;20(1):1–14.
103. Mónica GC, Marcela MCG, Astolfo CZC, Ricardo VB. Antiproliferative activity of total extracts from *annona squamosa*, *petiveria alliacea* and *punica granatum* on cancer cell lines. Pharmacologyonline. 2020;3:7–18.
104. Panzeri D, Guzzetti L, Sacco G, Tedeschi G, Nonnis S, Airoldi C, et al. Effectiveness of: *Vigna unguiculata* seed extracts in preventing colorectal cancer. Food Funct. 2020;11(7):5853–65.
105. Istiqomah MA, Hasibuan PAZ, Sumaiyah S, Yusraini E, Oku H, Basyuni M. Anticancer effects of polyisoprenoid from *Nypa fruticans* leaves by controlling expression of p53, EGFR, PI3K, AKT1, and and mTOR genes in colon cancer (WiDr) cells. Nat Prod Commun. 2020;15(4):1–8.
106. Esghaei M, Ghaffari H, Esboei BR, Tapeh ZE, Salim FB, Motevalian M. Evaluation of Anticancer Activity of *Camellia Sinensis* in the Caco-2 Colorectal Cancer Cell Line. Asian Pac J Cancer Prev. 2018;19(6):1697.
107. Asif M, Shafaei A, Abdul Majid AS, Ezzat MO, Dahham SS, Ahamed MBK, et al. *Mesua ferrea* stem bark extract induces apoptosis and inhibits metastasis in human colorectal carcinoma HCT 116 cells, through modulation of multiple cell signalling pathways. Chin J Nat Med. 2017;15(7):505–14