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Review

Plant-derived bioactive compounds in colon cancer treatment: An updated review

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ABSTRACT

Colon cancer is the third most predominant cancer caused by genetic, environmental and nutritional factors. Plant-based compounds are very well known to regress colon cancer in many ways, like delaying tumor growth, managing chemotherapy and radiation therapy side-effects, and working at the molecular levels. Medicinal plants contain many bioactive phytochemicals such as flavonoids, polyphenol compounds, caffeic acid, catechins, saponins, polysaccharides, triterpenoids, alkaloids, glycosides, phenols, quercetin, luteolin, kaempferol and luteolin glycosides, carnosic acid, oleanolic acid, rosmarinic acid, emodin, and eugenol and anthricin. These bioactive compounds can reduce tumor cell proliferation via several mechanisms, such as blocking cell cycle checkpoints and promoting apoptosis through activating initiator and executioner caspase. Traditional medicines have been used globally to treat cancers because of their anti-cancer effects, antioxidant properties, anti-inflammatory properties, anti-mutagenic effects, and anti-angiogenic effects. In addition, these medicines effectively suppress early and intermediate stages of carcinogenesis when administered in their active and pure form. However, traditional medicine is not very popular due to some critical challenges. These include poor solubility and absorption of these compounds, intellectual property-related issues, involvement of drug synergism, absence of drug-likeness, and unsure protocols for their extraction from the plant source. Using bioactive compounds in colon cancer has equal advantages and limitations. This review highlights the benefits and challenges of using bioactive compounds derived from plants for colon cancer. We have also discussed using these compounds to target cancer stem cell self-renewal, its effects on cancer cell metabolism, safety parameters, easy modulation, and their bioavailability.

1. Introduction

Cancer is one of the most dreadful non-infectious diseases that can drastically deteriorate an individual's life quality. Due to the rapid infusion of technological advancements, life-threatening genetic diseases like cancer have increased [1]. Day-to-day exposure to hazardous toxicants can alter the cellular system's standard mechanism and ultimately cause genetic damage. Also, a poor diet with insufficient fruits and vegetables and lifestyle factors such as smoking and alcohol can increase cancer risk. Cancer cells can rapidly spread to other organs through metastasis. Early-stage detection and treatment can only prolong the overall survival rates of lives or help in management instead of curing it completely. Among all the other cancers, colon cancer is the world's third most frequent cancer that initiates in the large intestine and extends to the lower part of the digestive system [2]. Genetic mutation, environmental or lifestyle factors, or bad food habits contribute to the pathogenesis of colon cancer. Three major mechanisms are involved in the carcinogenesis of colorectal cancer (CRC): chromosomal

Abbreviations: CRC, colorectal cancer; CDK, cyclin-dependent kinase; BCL2, B-cell lymphoma 2; BAX, BCL2-associated X protein; Apoptosis-inducing factor, AIF; Glutathione peroxidase, GPx; proliferating cell nuclear antigen, PCNA.

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instability, CpG island methylator phenotype and microsatellite instability [3]. Among environmental factors, nutritional aspects leading to obesity and energy intake are also the risk factor for colon cancer [4]. Recent studies have shown that several compounds derived from seeds, fruits, bark, roots and leaves of the plants have anti-carcinogenic properties [5]. They can regress colon cancer growth in many ways, such as by increasing superoxide dismutase level; decreasing the oxidative stress-mediated DNA damage; inducing cell cycle checkpoint arrest at the G1 phase, G1/S phase, S-phase and G2/M phase to enhance apoptosis; reducing anti-apoptotic protein levels such as BCL2 (B-cell lymphoma 2) and BCL-XL(B-cell lymphoma-extra large); reducing the expression of PI3K(phosphoinositide 3-kinase), AKT (Ak strain transforming) and MMP (matrix metalloproteinase) level; inducing the expression of several cell cycle inhibitors such as p53, p21and p27 and apoptotic markers such as BCL2-associated agonist of cell death, BCL2-associated X protein (BAX), Caspase3, Caspase7, Caspase 8 and Caspase 9 protein [4]. Use of natural sources such as berries, grape, plums, pomegranates, green tea, cruciferous, vegetables, soybean, tomatoes, garlic, turmeric, ginger, olive, whole grains, and mushrooms, garlic, and pomegranate can inhibit the development and colon carcinogenesis by promoting apoptosis and cell cycle arrest [6]. Around 35, 000 herbal bioactive compounds are obtained from plants, marine and other sources, which minimise the adverse effects of using modern technology to treat cancer, such as chemotherapy and radiological therapy [7]. The medicinal plants are the most reliable source of bioactive compounds for natural remedies that enhance the medicines to alternative systems as a green approach to treating CRC. The terpenoids, saponins, volatile oils, flavonoids, phenolics, quinones and alkaloids have a potent cytotoxic effect against CRC cells with lower risks and fewer side effects [8]. Chemotherapy is one of the best processes to treat colon cancer. Still, its application in developing countries is minimal, especially in rural areas, due to the limited facility and accessibility and lack of modern diagnostic tools [9].

Chemotherapy, however, has many limitations, like its side effects on normal cells and the chemoresistance property of CRC creates a significant issue in improving and managing CRC [10]. To compensate for these issues regarding the utilizing of chemotherapy, radiation therapy, immunotherapy, targeted therapy as well as surgery, phytotherapy comes as an alternative therapy where a variety of plant-derived bioactive compounds are used because of their anti-tumour and chemoprotective activity as well as very few side effects of treating colon cancer [11]. Some clinically tested naturally anti-cancer bioactive products include vinblastine, vincristine, podophyllotoxin, paclitaxel (taxol) and camptothecin[12]. However, few secondary plant metabolites such as flavonoids, phenolics, terpenoids, saponins, quinones, and alkaloids have shown potent chemoprotective activity against CRC cells through triggering apoptosis and cell cycle arrest, modulation of tumour-suppressive microRNA, inhibition of oncogene and anti-apoptotic factor [13]. This review describes the plant-derived bioactive compounds and their potential anti-cancer therapeutic effects. In addition, this review also discusses the mechanism of action of plant-derived compounds and their limitations and challenges as supplements [13].

2. Colorectal cancer

The prevalence of CRC was comparatively low in the 1950 s, and the incidence of the disease increased later because of unmet screening methods and lifestyles. The mass formation of a tumor develops when healthy cells in the lining of the colon or rectum grow out of control. A tumor could be primary or metastatic. The treatment of primary and metastatic colon cancer includes laparoscopic surgery, radiotherapy, immunotherapy, targeted therapy, and palliative chemotherapy has been developed [14]. Even though clinical advancements have been consistent in colon cancer studies, the cure or survival rate has not improved over the years.

2.1. Epidemiology of colorectal cancer

CRC is the third most common neoplastic malignancy in both men and women in Asia [15]. It accounts for 9.7% of all cancers collectively except non-melanoma skin cancer. More than 50% of the cases are from developed countries worldwide because of a fast-paced lifestyle and a significant shift in eating habits. Most cases come from patients above 50 or 60 at diagnosis [16]. The maximum number of CRC cases were reported in Australia and New Zealand, whereas the lowest number of cases were in Western Africa. In 2013, colorectal cancer was fourth in cancer-related deaths worldwide [17]. Compared to other Western countries, the prevalence rate of CRC is low in Asia, yet it has the highest number of prevalent cases [18]. According to global cancer statistics, in 2020, 19.3 million new incidences and 9.9 million deaths have been found due to CRC. The incidence percentage of CRC is 10%, and death caused by CRC is 9.4% [19]. According to the Global CRC burden study report, 1.93 million people have been diagnosed with CRC, and 0.94 million will die from CRC worldwide in 2020 [20]. One study has been performed in India to check the trends of CRC in the country. According to this study, CRC incidence has increased by 5.8% per 100,000 persons from 2004 to 2005 and 6.9% from 2012 to 2014 [21].

2.2. Pathophysiology of CRC

CRC often begins as tissue growth on the mucous membrane, known as polyps. The traits of colorectal cancer are developed as genetic mutations accumulate progressively. Genetic and epigenetic instability has been studied in neoplastic lesions in the colon (aberrant crypt foci, polyps, and adenoma) [22]. A polyp is a noncancerous growth that may develop on the colon or rectum's inner wall as people age. Polyps can become life-threatening if it is not treated early. In the early stage, CRC can be prevented by early detection and removal of pre-neoplastic adenomas. Multiple polyps have been found in colon cancer, such as tubular adenomas, villous adenomas, tubulovillous adenomas, serrated adenomas, hyperplastic and inflammatory [23,24]. Adenoma polyps or adenomatous polyps are the tissue growth with many chances of becoming cancerous. Most colorectal cancers arise at the aberrant crypt stage that progresses into early adenoma. This further develops into advanced adenoma and goes beyond 1 cm of growth when observed in the histology of a villus [25]. Colonoscopy is the procedure used to detect abnormalities in the large intestine. During a colonoscopy, the polyps are found in the colon easily as it has a bulge-like structure. Only 90% of polyps are found through colonoscopy easily, and the rest 10% of the polyps differ in their formation. The conventional adenomas have homogenous nature and cannot easily be differentiated from the normal histology of the section. But the molecular biology of these polyps is heterogeneous and can determine which adenomas will progress into colorectal cancer [26]. Few screening tools have already been established for detecting CRC in its early stages, such as colonoscopy, sigmoidoscopy, fecal occult blood test, and fecal immunohistochemical test, which are very sensitive compared to guaiac-based hemoccult tests [27]. Though much advancement happened in the early detection and removal of polyps from the colon, the incidence rate and CRC-related morbidity are increasing daily.

3. Causes of colorectal cancer

Healthy cells are grown and divided in an orderly way up to their hayflik limit, and after reaching this limit, cells die off. But cancer does not have any hayflik limit and divides indefinitely. Because of mutation, some genes converted to oncogene from proto-oncogene [28]. Many factors are involved in increasing the risk of colon cancer, such as older age, where peoples above 50 years of age are more prone to be affected by colon cancer and people younger than 50 years of age have a 4% chance [29]; peoples in the developing country who have started to use Western diets such as lower consumption of fibres and higher

consumption of animal proteins and fat [30]; personal history of CRC polyps [31]; inherited syndromes which came across through generations within the family can increase the risk of colon cancer such as familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer also lynch syndrome, mutY DNA glycosylase-associated polyposis which could increase colon cancer risk. Gardner Syndrome, Turcot's Syndrome and Peutz-Jeghers Syndrome [24,32], inflammatory bowel diseases such as ulcerative colitis and Crohn's disease can increase the risk of colon cancer [33]. A sedentary lifestyle [34], type-II diabetes [35], and lack of physical activity [36] can enhance the incidence of colon cancer. Excessive alcohol consumption leads to the accumulation of acetaldehyde in the body, damaging the DNA [37]. Smoking induces oxidative stress causing DNA damage, and may promote uncontrolled cell proliferation [38]. Radiation therapy during prostate cancer treatment may increase the chance of mutation of DNA of surrounding normal colonic epithelium, causes the progression of colon cancer [39], and consuming processed food after metabolising N-nitroso compounds can cause DNA damage which increases the risk of colon cancer [40].

4. Anti-cancer effects of plant-derived bioactive compounds and their mechanisms of action

Plant phytochemicals can inhibit tumorigenesis [41]. Medicinal plants contain many phytochemicals and bioactive compounds such as flavonoids, polyphenols, carotenoids, anthocyanins, genistein, resveratrol, caffeic acid, epigallocatechin, saponins, polysaccharides, triterpenoids, alkaloids, glycosides, phenols, quercetin, luteolin, rosmarinic acid, carnosic acid, emodin, eugenol kaempferol and luteolin glycosides [42]. These phytochemicals are derived from the plants' seeds, fruits, roots, and leaves. They can induce apoptosis through the mitochondrial pathway via releasing cytochrome C and/or caspase activation. They cause the formation of an apoptosis-inducing factor (AIF) [43]. Some of these compounds can induce the production of pro-apoptotic protein caspase-3 and BAX and inhibit anti-apoptotic factors [44]. They can interfere with activating the pro-inflammatory molecule nuclear factor κ-B (NF-kB) by blocking Iκ-B degradation [45]. They can induce cell cycle checkpoint arrest at different phases such as the G1 phase, G1/S transition, and G2/M transition by down-regulating cyclin-D1 and up-regulating p21 protein and inhibiting various cyclin-dependent kinase (CDK) such as CDK1, CDK 2, CDK 4, CDK 6, CDK 7, and CDK 9 [46]; suppress wnt/β-catenin pathway via inhibition of nuclear translocation ofβ-catenin; induce the expression of prometastatic matrix metalloproteinase (MMP) such MMP2 [47], MMP9 and survivin [48]; can inhibit different protein kinase such protein kinase-A (PKA), protein kinase-C (PKC), extracellular-signal-regulated kinase 1 (Erk-1) [45] and protein kinase-B(PKB) [49]; up-regulate the level of p53, Phosphatase and TENsin homolog (PTEN) [49] and anti-oxidative enzymes levels such as glutathione peroxidase (GPx) [47]. Some bioactive compounds interfere with the growth of CRC cells by alkylating DNA, inducing the generation of reactive oxygen species (ROS) [50]. Some act as an epigenetic regulator and causes degradation of DNA methyl transferase 3 A and histone deacetylase to suppress the CRC [51]; some of them can inhibit cyclooxygenase 2 (COX-2) activity; can inhibit proliferating cell nuclear antigen (PCNA), and insulin-like growth factor 1 (IGF-1) [52]; can inhibit multiple receptor kinases (RTKs) such as insulin-like growth factor receptor (IGFR) and ErbB3 [53]; inhibit epithelial-mesenchymal transition, migration and invasion [54]; inactivate polyadenosine diphosphate-ribose polymerase (PARP) by cleavage and inactivation of signal transducer and activator of transcription-3 (STAT3) [55]. Plants and their leading composites follow some of these mechanisms to inhibit the development of neoplastic growth in the colon. The purification of herbal components and affirmation of their bioactivity by relevant in vitro models, and clinical studies, may lead to the emergence of effective therapeutics for colon cancer treatment. According to Aiello Pet al., grape, soybean, green tea, garlic, olive, and pomegranate are the most efficient for treating colon cancer owing to their anti-cancer properties [6]. Studies on fruits, seeds, leaves, and plant roots extracts from the different plants have already validated these assumptions using in vitro and in vivo techniques.

Bioactive compounds from plants can intervene in carcinogenesis at various stages by inhibiting, delaying, or reversing before the tumor attains invasive malignancy. Traditional medicines have been used globally to treat cancers because of their anti-angiogenic effects, anti-invasive effects, anti-proliferative effects, antioxidant properties, anti-inflammatory properties, and anti-mutagenic effects [56].

5. Proven medicinal plants with bioactive compounds

5.1. Anthocyanin-rich phenolics from Podocarpus elatus

Podocarpus elatus, also called the *Illawarra plum*, is found in eastern New South Wales, East Australia, and Queensland. The seeds of the fruit are purple-blue like a berry, having a single oval at its base [57]. The *Podocarpus elatus*is are rich in antioxidants and anthocyanin-rich phenolics. The mechanisms of the anti-proliferation activity were studied using *Illawarra plum* extract on the colon cancer cells. The tumorigenic human colonic (HT-29) and non-tumorigenic young adult mouse colonic (YAMC) cells were dosed with the polyphenolic-rich extract of this fruit. This extract can decrease the cancer cell viability dose-dependently [58]. This extract increased the apoptosis rate by 2-fold and delayed the growth in the S phase of the cell cycle of HT-29 cells. *Illawarra plum* extract also decreased telomere length by down-regulating the telomerase activity. Morphological changes in the HT-29 cells have also been observed in the cytoplasmic vacuoles of the cells after the treatment with the extract. This extract elevated the activity of histone deacetylase (HDAC) and class III HDAC. Recent studies have found that the plum pine decreases the colon cancer cells' growth rate, maximizing the cells' death rate by generating autophagy, which is mediated via alterations in the cell cycle [59].

Since berries contain excess phenolic compounds, most anti-cancer studies were carried out using their extracts. The Illawarra plum has been a significant source of extracts of medicinal importance for many years, but their use has been limited due to slow-paced research in the nutraceuticals domain. The richness of anthocyanins in the Illawarra plum enhances its oxygen radical scavenging ability by 146% compared to similar fruits [60].

5.2. Methanolic extract of Achyranthes aspera

Achyranthes aspera belongs to the family of *Amaranthaceae* and is well known for its medicinal properties. It has been used as a traditional medicine for many years in Ayurveda because of its anti-cancer properties. In addition, it is used to treat or manage the pancreas and colon tumour cells.

Aspera is used alone or in combination with some other anti-cancer treatments. *In vitro* studies were conducted to test the anti-proliferative properties of methanolic extract of *A. aspera* leaves. The extract modifies the cell cycle regulation and intervenes in the metabolism of tumors. The transcription of metalloproteases (MMP-1 and 2), angiogenic factors such as vascular endothelial growth factor (VEGF)1 and VEGF-2, and inhibitors of MMPs such as tissue inhibitor of metalloproteinases 2 (TIMP-2) are suppressed by the leaf extracts [61]. The compounds present in *Achyranthes aspera* has many beneficial properties which can be used for treating stones in the bladder, piles, stomach troubles, wound, and cancer because of the presence of betaine, oleanolic acid, and achyranthine [62]. The extracts of *Aspera* leaves have ethnomedicinal properties such as diuretic, wound-healing, hepatoprotective, antioxidant, anti-depressant, and cancer chemotherapy. The extracts derived from the plant's roots have immunomodulatory and anti-inflammatory properties. The extracts suppress colon cancer cell proliferation in a dose- and time-dependent manner. The plant extract induces apoptosis of the COLO-205 cells by altering the mitochondrial

pathways and blocking the S phase of the cell cycle [63].

5.3. Ellagic acid from Terminalia ferdinandiana

The *Terminalia ferdinandiana*, the billygoat plum, belongs to the *Combretaceae* family. High vitamin C content makes it more suitable for traditional medicines[64]. High antioxidants have been tested in the kernels that contribute as preventive medicines against many degenerative diseases like cancer, diabetes, cardiovascular diseases, neural degeneration, and obesity. The antioxidants present are phenolic compounds and vitamin C [65]. Phenolics are associated with signal transduction as they communicate with enzymes or receptors, which is the basis of the normal function of human molecular biology. Common plant phenolic compounds are tannins, flavonoids, gallic acid, and anthocyanins. The primary application of *T. ferdinandiana* fruit extract is utilized in pharmaceutical and nutraceutical industries and the cosmetic industry because of their high vitamin C content [66]. Benzoic acids, flavanols, and flavanones are also abundant in the fruit. *T. ferdinandiana*is also a source of ellagic acid and gallic acid, which are known for their anti-carcinogenic and antioxidant properties. The fruit also contains a high amount of chlorophyll a and chlorophyll b in addition to lutein and vitamin E. It is also a reliable source of essential minerals like potassium, sodium, manganese, copper, magnesium, zinc, calcium, iron, phosphorous, and molybdenum[67].

5.4. Ethanolic extract of Withania Somnifera

W. somnifera, popularly known as Ashwagandha in Ayurvedic medicine, is a well-established medicinal plant with anti-cancer properties due to the presence of withanolides, a steroidal substance found in the leaves and roots of this plant [68]. They are rich in bioactive compounds, and experimental studies prove that they improve rats' stamina because of their immunomodulatory properties. The anti-cancer properties of *W. somnifera* root extracts were observed in Chinese Hamster Ovary (CHO) cells [69]. Every ayurvedic medicine consists of extracts from *W. somnifera* because it has anxiolytic effects, antioxidant properties, anti-arthritic effects, and anti-inflammatory properties. Withanolides have successfully inhibited cancer cells in urethane-induced lung adenoma, uterine fibroids, and dermal sarcoma. The long-term treatment with Ashwagandha extracts keeps tumor growth in control. Additionally, insilico testing with anolide on multiple biological targets led to positive results [70]. However, the pharmacological application of *W. somnifera* extracts is yet to be commercialized. Ashwagandha decreases the expression of pro-inflammatory cytokines like IL-1β, IL-6, STAT-2, IL-8, and Hsp70 while up-regulating the expression of PI3K, Cyclin D and c-myc, caspase 6, and p38 MAPK. Consequently, this results in significant modification in the JAK-SAT pathway, which controls the signalling of MAP kinase and functions of programmed cell death [71]. *W. somnifera* root extract inhibit citric acid cycle enzymes, such as isocitrate dehydrogenase, succinate dehydrogenase, malate dehydrogenase, and α-keto glutarate dehydrogenase in colon cancer-induced Swiss albino mice [72].

5.5. Catechins from Camellia sinensis

Camellia sinensis is a popular plant producing caffeinated tea from its tender leaves and buds. It is a shrub with multiple varieties, one of them found in the Assam region of India. Green tea is loaded with benefits and is known to have bioactive compounds that actively benefit the human body[73]. Tea extracts are highly rich in flavonoids and phenolic compounds and have anti-proliferative effects on colon cancer cell lines. The extracts induce apoptosis in the HT29 colon cancer cells by increasing the caspase3, caspase7, caspase8 and caspase9 [74]. Clinical evidence has shown that catechins are one of the major compounds found in *C. sinensis* with beneficial effects on many human diseases. The primary catechin is epigallocatechin-3-gallate (EGCG) which acts as an antioxidant, anti-angiogenic, and anti-tumour agent. EGCG has chemopreventive activities as it induces apoptosis, arrests cell growth, activates killer caspases, and suppresses the oncogenic transcription factors. In addition, EGCG acts on multiple signal transduction pathways like P13/AKT, JAK/STAT, and MAPK [75]. Black tea extracts from *C. Sinensis* contain polyphenol-rich compounds such astheaflavins and thearubigins, and flavanol-3–ol are potent anti-oncogenic compounds. These extracts inhibit the growth of HCT-116 colon cancer cell lines in a dose-dependent manner by reducing the expression of COX and blocking the G2/M phase transition [76]. One study investigated the leaf extract of *C. Sinensis plant* on colon cancer cell lines like HT-29 in micromolar concentration[77]. They reported a 1.9-fold increase in apoptosis of the tumor cell and a 3-fold increase in the apoptosis of endothelial cells. In addition, the leaf extracts can suppress the expression of VEGF and ERK-1, and ERK-2 [77].

5.6. Quercetin from Olea europaea

Olea europaea, commonly known as the olive tree, is found in European and Mediterranean countries. Olive leaf extract is known for many traditional remedies because it contains various bioactive compounds that are antioxidant, anti-inflammatory, hypoglycemic, hypocholesterolemic, and anti-hypertensive agents. Olives are rich in flavonoids like quercetin, secoiridoids, and triterpenes [78].

The effect of quercetin was studied using human colon cancer cell line Caco-2, and the data showed that it effectively reduced the proliferation and differentiation of these cells. In addition, the study indicated that higher microgram concentrations of quercetin from fruit extracts of *O. Eurpaea* effectively decreased the differentiation of colon cancer cells [79]. Ethanolic extract of olive leaves has already been studied for its antioxidant and anti-cancer potential [80]. The study indicated that hepatic and colon cancer cells are sensitive to specific concentrations of olive fruit extracts. In addition, flow cytometric analysis has shown that the compounds arrest the cell cycle of colon cancer cells at S-phase. Ultimately, this triggers cell death, further reducing tumur cell proliferation, migration, and invasion [81].

5.7. Curcumin from Curcuma longa

Curcuma longa is a common rhizome from the *Zingiberaceae* family, the primary source of the household spice called turmeric. It is a common kitchen spice used all over India and has numerous health benefits. Curcumin is the main bioactive compound with antioxidant, anti-inflammatory, anti-proliferation, anti-viral, and anti-fungal properties [82]. Curcumin has chemopreventive activity against multiple colon cancer cell lines like HT-29, HCT116, HCT15, and DLD1 using in vitro and in vivo techniques. Furthermore, Curcumin has an epigenetic effect on lung and oesophageal cancer 1 (DLEC1) by modifying the expression of DNA methyltransferases and histone deacetylases, thereby inhibiting the growth of HT-29 colon cancer cells [83]. It can also inhibit cell proliferation by blocking the G1 phase transition and the G2/M phase transition. Furthermore, up-regulating the p53 level causes the breakdown of PARP and thereby induces cellular senescence of HCT-116 colon cancer cell lines [84]. In addition, it exerts anti-cancer activity by inducing the activation of the pro-inflammatory molecule NF-κB through degradation of I-κB [85], inducing ROS generation and down-regulating the expression of E2F4 related genes such as cyclin A, p21 and p27 [86].

Many synthetic curcumin analogues, such as IND-4, FLLL, GO-Y030, and C086, were synthesized [87]. The cytotoxicity of these analogues was studied individually on colon cancer cell lines and in combination with existing anti-cancer drugs like 5-fluorouracil, tolfenamic acid, dasatinib, and resveratrol. The combination showed better efficiency in treating colon cancer than individual analogues [87]. In addition, the preclinical studies in 3D cell culture showed that ethanolic extracts of the rhizome inhibited spheroid formation in HCT116 [88].

5.8. Alkaloids from Annona muricata

Annona muricata, commonly known as soursop, is a tropical plant with proven medicinal benefitsas per the traditional use of its parts like leaves, fruit, seeds, bark, andfruit. The effect of ethyl acetate extract (EAE) of annonamuricataleaves containing a high amount of alkaloids, flavonoids, terpenoids, and otherphytochemicals has been studied on HT-29 and HT116 cells by using MTT andflowcytometric analysis. EAEs of leaves showed anti-cancer activity by inducingapoptosis through cell cycle arrest at the G1 phase, causing excessive ROSgeneration, disrupting mitochondrial membrane potential, releasing cytochromeC, and activation as initiator and executioner caspases such as caspase3,caspase7, caspase8,caspase9 and down-regulation of anti-apoptotic Bcl2 protein [89].

Annona muricata is also the source of several other bioactive compounds like acetogenins and annomuricin, having a cytotoxic effect on colon cancer cells. These compounds can kill colon cancer cell lines in lower microgram concentrations. In addition, they suppress the production of ATP molecules and NADH oxidase in cancer cells affecting the invasion and migration of the cells [90].

5.9. Emodin (natural anthraquinone) from Aloe vera

Aloe vera falls under the *Aloeaceae* family, a drought-resistance xerophytic succulent plant mainly found in warm and dry places (desert and coastal areas) of Asia, Africa, America and Europe. It has a powerful anti-inflammatory effect owing to the anthraquinone and various antioxidants such as α-tocopherol, vitamin C, tannins and others [91]. Emodin is one type of anthraquinone extracted from the Aloe vera gel, which has a cytotoxicity effect on SW480 and SW620 colon cancer cell lines. It causes the deregulation of the Wnt/β-catenin signalling pathway; it reduces the expression of EMT genes such as snail and vimentin, induces apoptosis by decreasing the expression of mRNA of C-myc, PCNA, cyclin-D1 and also reduces MMP2 and MMP9 level which are involved in migration and invasion [92].

5.10. Water extracts of Salvia officinalis and Salvia fruticosa

Both *Salvia officinalis and Salvia fruticosa* plants are found in the Middle East and Mediterranean areas and belong to the Lamiaceae family. These plants are rich in a wide range of bioactive compounds such as alkaloids, phenolic compounds, glycosides derivatives, a variety of carbohydrates, steroids and terpenoids [93]. Water extracts of *Salvia officinalis and Salvia fruticosa* are known as sage extracts and are highly rich in phenolic compounds. The major phenolic compounds are rosmarinic acid and various luteolin derivatives. Effects of sage extracts and the rosmarinic acid showed the anti-proliferative and anti-apoptotic effects on HCT15 and CO115 colon cancer cell lines. In addition, these extracts reduce the growth of CRC cells by inhibiting the phosphorylation ERK [94]. Another study showed that sage extracts and rosmarinic acid impede the development of HCT15 cells by inhibiting the KRAS oncogene, thereby downregulating MAPK/ERK signalling pathway [95].

5.11. Medicinal properties of Moringa oleifera

Moringa oleifera, a common name is drumstick found in South Asia, belongs to the *Moringaceae* family primarily used as a vegetable highly rich in various bioactive compounds such as phenolic acids, isothiocyanates, tannins, flavonoids, and saponins [96]. Extracts made from its leaves, bark and seeds were investigated. The leaves and bark extracts have greater anti-cancer efficacy than the seed extract. Eugenol, a phenolic compound in these extracts, inhibits cancer cell growth by targeting E2F1/surviving [97]. In addition, these extracts induce apoptosis by blocking the G2/M phase transition [98]. One study has shown that when eugenol in nanoemulsion induced apoptosis in HTB37 colon cancer cells mediated by ROS generation [99].

5.12. Ethanolic extracts of Chamaecyparis obtuse

Chamaecyparis obtuse is a tropical tree belonging to the *Cupressaceae* family, found in Japan, Korea and North-East China; it grows in cold and warm climatic conditions. Leaf extracts of *Chamaecyparis obtuse* plants have been used for their potent anti-cancer, anti-inflammatory and anti-allergic activity [100]. This plant is rich in phytochemical compounds such as phenolic compounds (quercetin), phenolic glycosides and essential oils (α-terpene and limonene). The ethanolic extract of *Chamaecyparis obtuse* leaves showed an inhibitory effect on the growth of HCT116 colon cancer cell lines in a dose-dependent manner [101]. The methanolic extract at 1.25 μg/mL concentration exhibited significant growth inhibition of HCT116 cells [101]. This extract contains one major compound, anthricin, which belongs to the naturally occurring flavonolignan group. This anthricin causes the induction of apoptosis by activating the c-Jun N-terminal kinases(JNK) signalling pathway, thereby inhibiting the growth [101].

5.13. Carnosic acid from Rosmarinus officinalis

Rosmarinus officinalis, a familiar name is *rosemary*, belongs to the *lamiaceae* family, sun-loving shrubs, native to the Mediterranean region, England, Spain, Turkey, France, Mexico, South-Eastern Spain and limited extent to India also [102]. Rosemary leaf extract contains one primary polyphenolic diterpene compound known as carnosic acid. Carnosic acid plays an essential role in the induction of apoptosis and inhibits the proliferation of HCT116 and SW480 colon cancer cell lines. In addition, this compound targets the Nrf2/ARE signalling pathway, which up-regulates Nrf2 expression and promotes nuclear translocation, thereby making a complex with an antioxidant response element [103].

5.14. Oleanolic acid from Vitis vinifera

Oleanolic acid isolated from *Vitis vinifera* is a grapevine that falls under the *Vitaceae* family. These grow in long warm summers and rainy winters and are mostly found in Asia, North America and Europe [104]. Grape seed extract contains various bioactive compounds such as flavonoids, proanthocyanidins, polyphenol, anthocyanins, resveratrol, and oleanolic acid. These extracts have antioxidant, anti-proliferative and anti-bacterial activity. Owing to these properties, these extarcts are used as a therapeutic agent to maintain the normal function of the heart, liver and kidney [105]. Ethyl acetate extract of grape seed contains oleanolic acid, one type of aglycone isolated from triterpenoid saponins. Oleanolic acid has both anti-oxidative and anti-cancer properties. Oleanolic acid inhibits the cell proliferation of HCT116 colon cancer cell lines, assessed by the cell viability assay [106]. It has been reported to inhibit the cell proliferation of HCT116 colon cancer cell lines, which was evaluated by a cell viability assay [106]. Table 1 summarises various bioactive compounds, their sources, and their activities.

6. Advantages of plant-derived compounds

Plant-based bioactive compounds have an array of benefits which are researched for having a potential effect on health. Many in vitro epidemiological studies have shown promising results related to compounds like polyphenols, flavonoids, plant sterols, salicylates, and glucosinates [115,116]. Fig. 1 describes various ways in which a plant-derived compound is advantageous for use in colon cancer treatment.

6.1. Targeting cancer stem cell self-renewal

Natural food products affect three crucial epigenetic factors DNA methylation, microRNA expression, and histone modification. Plant-derived compounds are known to inhibit the cancer stem cells' self-renewal capability, and this strategy can potentially reduce the

Table 1
List of bioactive compounds, their sources and their activities.

Compound	Plant Source	Extract Source	Activity	References
Anthocyanin-rich phenolics	*Podocarpus elatus*	Fruit	Alters mitochondrial pathways and blocks the S phase of the cell cycle	[57]
	Ribus nigrum	Whole fruit	Induces ROS generation, and apoptosis via caspase3 activation and inhibits MMP2 and MMP9 expression	[107]
	Berberis Lycium	Root	antioxidant and cytotoxicity effect	[108]
Phenolic compounds	*Achyranthes aspera*	Leaves	Suppresses angiogenic factors, induces apoptosis, and anti-proliferative properties	[61-63]
	Pisum sativum	leaves and buds	potent cytotoxic effect against colon cancer cells	[109]
	Siberian ginseng *(Eleuthrococcussenticocus)*	Root	Induces apoptosis	[110]
Ellagic acid	*Terminalia ferdinandiana*	Kernels	Reduces oxidative stress by free radical scavenging activity	[59,65-67]
	FragariaXannanasa	Fruit, leaves, roots		
	Euphoria longana	Seed		
	Gleditsia sinensis	Thorn		
Withanolides	*Withaniasomnifera*	Leaves	Downregulates inflammatory pathways control MAP kinase signalling, modifies JAK-STAT pathway	[68-70]
Catechins	*Camellia sinensis*	Leaf	Acts on multiple signal transduction pathways, increases apoptosis and suppresses VEGF expression	[74,76,77]
	Phyllanthus emblica	Fruits, Seed, Pulp	Suppress cell proliferation by targeting the Wnt/β-catenin pathway, downregulate cyclinD1c-MYC	[111]
Flavonoids	*Morus alba*	Leaf	Induce cell cycle arrest and apoptosis	[112]
Quercetin	*Olea europaea*	Fruit	Decreases cell differentiation, arrests cell cycle at S phase	
	Phytolacca americana	Root		
	Salix aegyptica	Berk		
	Phoenix dactylifera	Fruit		
Curcumin	*Curcuma longa*	Root	Inhibits spheroid formation, free radical scavenging	
	Curcuma amada			
Alkaloids	*Annona muricata*	Leaf	cell cycle arrests at the G1 phase induce apoptosis, accumulates ROS, disrupt mitochondrial membrane potential	[89]
	Annona squamosa			
	Eupatorium cannabium	Aerial parts		
	Codonopsis lanceolata	Root	cell cycle arrest at G0/G1 phase, induce expression of p53, caspase3	[113]
Emodin (natural anthaquinone)	*Aloe vera*	Leaves	Induce apoptosis by reducing the activity of PCNA, c-Myc and cyclin-D1deregulate; Wnt/β-catenin pathway; inhibit the expression of EMT-specific genes	[92]
Rosmarinic acid (phenolic compounds)	*Salvia officinalis*	Leaf	Iinhbitit the growth of HCT15 and CO115 by downregulating the MAPK/ERK signalling pathway	[9,95]
	Salvia fruticosa			
Eugenol	*Moringa oleifera*	Leaves, bark and seed	Induce apoptosis by cell cycle arrest at the G2/M phase	[98]
	Clove *(Syzygiumaromaticu)*	Cloves bud	Induce apoptosis and autophagy by inhibiting the phosphorylation of PI3K/AKT/mTOR signalling pathway	[114]
Anthricin (flavonolignan)	*Chamaecyparis obtuse*	Leaf	Causes apoptosis by activating the JNK signalling pathway	[101]
Carnosic acid (polyphenolic diterpenoid)	*Rosmarinus officinalis*	Leaf	Inhibit proliferation by activating Nrf2/ARE signalling pathway	[103]
Oleanolic acid (triterpenoid saponins)	Grapes *(Vitis vinifera)*	Seeds	Induce apoptosis of HCT116 cell lines	[106]

proliferation of colon cancer. Dietary compounds actively inhibit the Wnt/Beta-catenin pathway that can impact the self-renewal of cancer stem cells. Curcumin from Indian spices, soy isoflavones like genistein, extracts from cruciferous vegetables, EGCG from green tea, resveratrol in grapes or berries, lycopene from tomatoes, and piperine from black peppers affect signalling pathways responsible for self-renewal of cancer stem cells. These compounds regulate dickkopf-1, CDK6, and sFRP2 quenches proliferation and quiescence[117].

Cancer stem cells are of utmost importance because studies suggest that they are not affected by radiation and chemotherapy. Such a phenomenon allows cancer recurrence at secondary sites, and it is important to target them using plant bioactive compounds. Also, the aggressiveness of pancreatic cancer can be traced back to the dysregulation of the self-renewal of cancer stem cells. In such cases, using a common polyphenol and flavonoids like quercetin found in many fruits and vegetables effectively reduces the stemness of the cell [118]. In addition, quercetin reduced aldehyde dehydrogenase-1 activity alongside inducing apoptosis.

Furthermore, quercetin reduced the expression of proteins that promoted the growth of cancer stem cells-derived xenografts. It also reduced the expression of genes involved in angiogenesis [118]. Another study highlighted the efficacy of pomegranate extracts against mammary cancer cell line WA4. This particular cell line has cancer stem cells as its characteristic property due to the high percentage of cancer stem cells in the cell line. The treatment using pomegranate extract showed a blockage in the cell cycle at the G_0/G_1 phase, and caspase-3 was activated, which further induced apoptosis [119]. The extract consisted of ursolic acid, ellagic acid, and luteolin. These bioactive compounds also yielded fruitful results when tested upon pancreatic cancer cell lines like PANC-1 and AsPC-1 [120].

Similarly, extracts from *Maclurapomifera* from the *Mulberry* family inhibit the growth and invasion of glioma cancer stem cells. The pomiferin, the flavonoid extract, significantly reduces the viability of the cell and decreases CD133 + stem cells. Moreover, the expression of genes that are related to stemness, such as Bim1, Nestin, and Nanogalso reduces after treatment with the flavonoid [121].

6.2. *Effects of phytochemicals on cancer cell metabolism*

Nutritional intervention to improve cancer chemotherapy is beneficial because bioactive compounds affect cancer metabolism in helpful ways. Some phytochemicals that play a significant role in metabolic

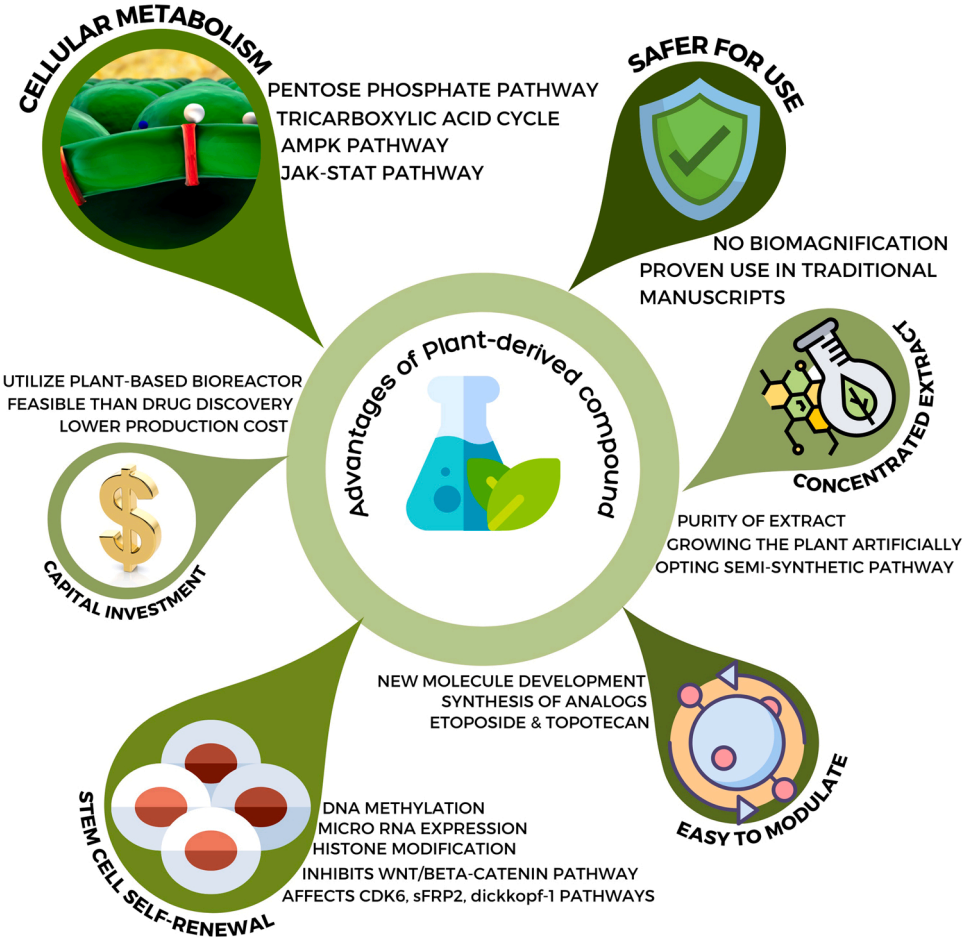

Fig. 1. Advantages of using a plant-derived compound in colon cancer treatment.

pathways are discussed in this section. Nutrients like sulfur, vitamin B, iron, magnesium, manganese, and cysteine actively modulate mitochondrial enzymes and biogenesis. These phytochemicals protect cells from mitochondrial damage that ultimately prevents the growth of cancer cells [122]. For example, epigallocatechin and genistein affect the pentose phosphate pathway, tricarboxylic acid cycle and lactate production. This promotes apoptosis and attenuates tumor growth.

Similarly, green tea polyphenols like EGCG work on the AMP-activated protein kinase pathway, which controls cellular energy, cell cycle progression, protein synthesis, and cell growth. Modulating these pathways will ultimately cause apoptosis. This is also why many nutritionists encourage the use of olive oil because it has abundant polyphenols. Also, resveratrol in fruits and vegetables readily affects ROS release and oxidation reaction within the cells. These components scavenge the ROS from the cells and prevent the microenvironment development for tumor growth.

Phenolic compounds have also shown promising results in modulating metabolism in different cancer cell lines. Apigenin is a commonly found flavone in fruits and vegetables with significant antioxidant and anti-cancer properties [123]. Apigenin downregulates the glucose uptake, thus affecting the growth of tumors. In short, apigenin downregulates GLUT-1 mRNA in pancreatic cancer cells. Hence, there is a drop in glycolytic flux and ATP. Moreover, this does not affect the expression of several other glycolytic enzymes. In several cases, apigenin-induced apoptosis resulted in cell growth inhibition and increased sensitivity toward cancer chemotherapy [124].

Similarly, curcumin, a common dietary spice, decreases the expression of GLUT1 mRNA in cancer cells, thus reducing carbohydrate availability to these cells and thus affecting the invasiveness. The effect on this metabolic pathway ultimately affected the glucose uptake, ATP production, and lactate production in HCT116 and HT29 cells. The study also suggested mitochondrial-mediated apoptosis after confirming curcumin-induced hexokinase 2 dissociation from mitochondria. While many studies indicate that other glycolytic enzymes remained unaffected, a study based on oesophagal cancer cells using curcumin treatment suggested that the micromolar concentration of the compound had an impact on wider glycolytic enzymes. As a result, it decreased GLUT4, hexokinase 2, P 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 2, and pyruvate kinase M2 at the protein level [125].

6.3. *Ethnomedicine is safer to use*

Botanical sources have been used for drug discovery because the ethnic relevance of the plants makes them safer for treating humans. In the long-term use, traditional medicine is preferred because it doesn't have biomagnification of the chemicals in the body. Bioactive compounds from plants like *Rauwolfia serpentina* and *Digitalis purpurea* are perfect examples of natural compounds used for drug discovery and synthesis. However, plants with no history of clinical trials or use on humans are comparatively risky because their toxicological profile is unknown [126].

6.4. *Modulation of compounds with toxic effects*

The study of natural plant compounds is used as a strategy to give rise to new potential drugs that help treat colon cancer. Even if the compound turns out to be toxic, it creates a scope for the development of a novel molecule which is simulated to work appropriately in the human

body [127].

Podophyllin extracted from *Podophyllum hexandrum* is toxic, preventing it from being used in cytotoxic doses. Etoposide is synthesized, and it is being used as a potential anti-cancer agent. In addition, etoposide showed anti-proliferative effects on wild-type p53 liver carcinoma in HepG2 cells and colon cancer, HCT-116 cells [128]. Similarly, camptothecin extracted from *Camptotheca* was toxic and ineffective. Hence, new anti-cancer agents named topotecan and irinotecan were formulated based on the cytotoxic activities of camptothecin. The ability of these drugs to reduce the xenograft size in metformin-sensitive (HT29) cells, metformin-resistant (SW620), and COLO205 cells is very promising [129].

6.5. Rich source of concentrated compounds with bioactivity

Naturally, isolated compounds are more promising in delivering the bioactive compound in its exact form. These compounds are readily available in the plants they are found in. The concern related to the exploitation of the plants and natural resources can be overcome with the help of growing the plants in an artificially created environment. Similarly, the drug can be synthesized in a semi-synthetic form to overcome the challenges and limitations related to its toxicity.

7. Challenges of using plant-derived compounds

As much as plant-derived bioactive compounds are readily available and seem fascinating to enter research and development, it is also necessary to explore the several challenges around them. These challenges must be addressed to make it eligible for clinical trials. However, the biggest challenge is related to approval of the drug for commercialization because enough resources are unavailable. Since some compounds cannot be synthesized in a semi-synthetic manner or by growing or engineering the plant artificially, this will increase the product's dependency on natural resources. As per the reports, nearly 25,000 plants will go extinct, which imposes an ethical issue for extracting bioactive compounds from plants. In addition, there is still a lack of sufficient clinical data and their mechanisms of action. Finally, the bioactive compounds have side effects, solubility and absorption issues that will be discussed in this section. Fig. 2 describes the significant challenges of using the plant-derived compound in colon cancer treatment.

7.1. Solubility and absorption of the plant-derived bioactive compounds

The main problem with the plant-derived compounds is their bioavailability. The absorption of these bioactive compounds through the gut is not investigated well. In addition, these compounds are not soluble properly in the systemic fluid, which can raise a question about their potency. In addition, not all phytochemicals are stable in a systemic environment, preventing the compound from being available to the cancer cells at therapeutic levels [130].

Advanced methodologies such as encapsulating drugs in micro and nanocapsules are being adopted. For example, we can look at administering vinca alkaloids encapsulating in micro and nanocapsules using liposomes and micelles for better bioavailability. In the last few years, many drugs have been combined with nano polymers, nano micelles, and nanoconjugates for targeted drug delivery to cancer cells. By conjugating these drugs with polymeric vehicles, it becomes easier to fight other issues like circulation half-life and molecular concentration in blood. Chitosan particles, hyaluronic particles, silica nanoparticles,

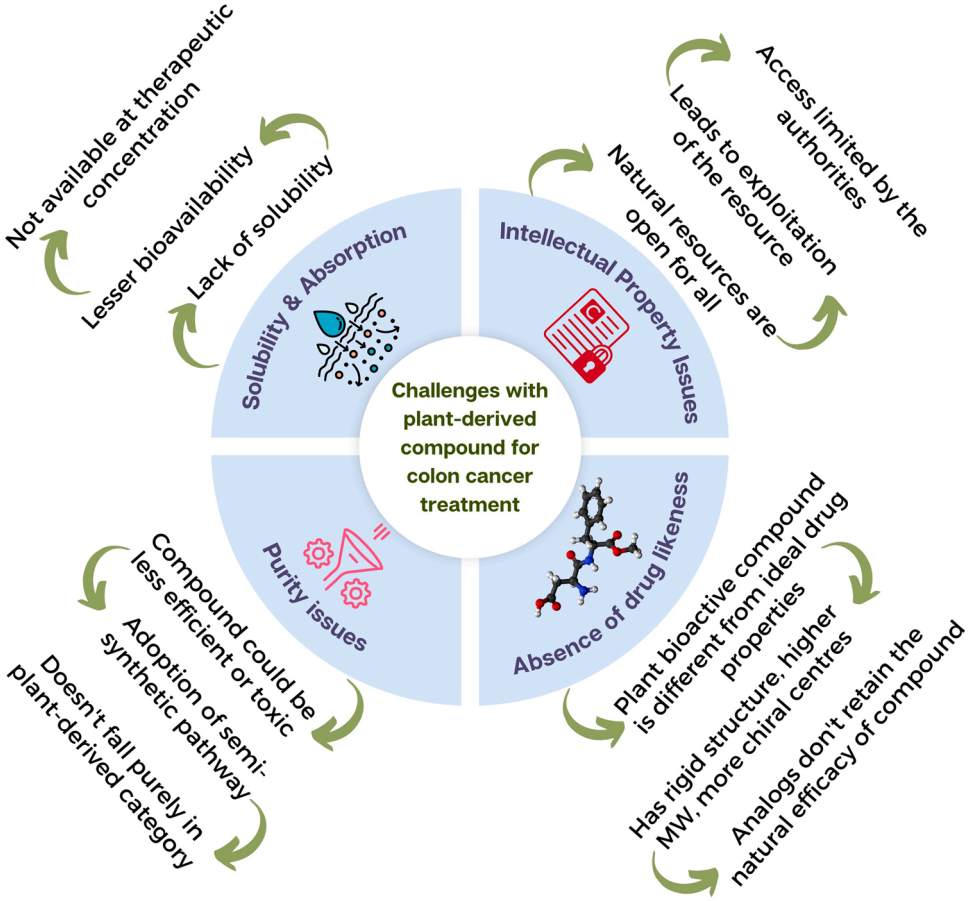

Fig. 2. Major challenges associated with using the plant-derived compounds in colon cancer treatment.

and gold nanoparticles are actively being utilized to deliver the drug.

7.2. Intellectual property rights of natural resources

Over the last few decades, natural resources have been protected by several modifications in intellectual property rights. When the leads are mentioned in traditional medicines, it becomes mandatory not to claim the product or derived product as a novel therapeutic. This also imposes limitations on research and development or modifications that can be done on the compound. These regulatory norms impose many challenges in the commercialization phase because it limits access to the main lead. This creates a considerable lag in developing active compounds or utilising semi-synthetic methodologies to improve the compound's therapeutic efficacy [131].

7.3. Drug synergism in colon cancer

Drug synergism has always been an exciting concept regarding increasing the efficacy of any therapeutic agent. Unfortunately, plant-derived compounds are less effective when administered as a single molecule. Combining the drug with conventional chemotherapeutic compounds is essential to enhance their cytotoxicity toward cancer cells or cell lines. This can remove the drug from the category of "plant-derived bioactive compound." However, the medicines may not be entirely natural and will retain the side effects of chemical compounds. This eradicates the use of clinically approved plant-based compounds for colon cancer when the final product lacks efficacy [132].

7.4. Absence of drug-likeness

Naturally-derived compounds have a chemical characteristic that differentiates them from other chemically synthesized drugs. These are the main criteria of the compound for approval of its clinical trial. On the other hand, the drug's chemical composition or internal characteristics imposes challenges in developing its analogues [133]. Characteristic features of compounds derived from natural products involve properties like having more chiral centres, sterically complex structure, more number of oxygen atoms, molecular rigidity, higher molecular weight, diversity of ring systems, and more number of hydrogen bond donors. But, to achieve drug-likeness, the naturally derived compounds' requirements differ from what they possess. An ideal drug has molecular characteristics that include lower molecular weight, a sterically stable and less rigid structure, five or fewer hydrogen bond donors and ten or fewer hydrogen bond acceptors.

All these factors contribute to the compound's bioavailability and encourage the development of its analogue. For natural compounds, it becomes very tough to change the draggability criteria and improve their efficacy alongside retaining the advantages of their natural origin [134]. Many natural products are biologically efficient and have an impressive profile when their absorption, distribution, metabolism, excretion, and toxicity are tested. However, these drugs are not likely to reach phase II of a clinical trial if they do not satisfy the drug-likeness criteria. This is one of the most significant disadvantages to deal with and a major contributing factor in slowing down the research and development of the naturally-derived bioactive compound.

8. Other possible limitations of using phytochemicals

The use of phytochemicals can be both advantageous and disadvantageous in preventing cancers. At the same time, certain phytochemicals can act as carcinogens or tumor promoters. The toxicity index of phytochemicals has not been investigated well enough in a clinical setting. Therefore, phytochemicals are not yet approved for further clinical application for cancer treatment. Some phytochemicals have a toxic effect on humans and may act as an antinutrient that stops the absorption of the essential nutrient. Also, phytochemicals face many methodological flaws like the small sample size, trial duration, and lack of control during clinical trials. Using traditional plants as supplementary with other medicines may cause adverse drug reactions, even life-threatening.

The FDA does not have a suitable protocol for testing and approving traditional plants' phytochemicals. Also, the route of administration can be questionable because plant-derived compounds are readily biodegradable. For example, male *podocarpus* spp. is highly allergic, and its stems, pollens, and flowers are poisonous. As the male podocarpus blooms, it releases cytotoxic substances retained in its extracts. Ashwagandha should be avoided in treating prostate cancer, as it increases testosterone levels.

Similarly, *achyranthens aspera* should be used with caution as it may cause severe skin infections. Excess intake of extract of this medicinal plant may also cause nausea. High oxalates containing Kakadu plum may cause Crohn's disease, hyperparathyroidism, ulcerative colitis, and renal tubular acidosis. Several phytochemicals studied for their anti-cancer properties at preclinical stages do not showcase proper molecular interaction with different signalling molecules. Many techniques like nanoparticle conjugated targeted drug delivery are being developed to make the bioactive compounds available for the tissues. The phytochemicals studied for cancer are at a very early stage for their use as an anti-cancer agent. The well-controlled and large-scale clinical trials must confirm phytochemicals' safety, effects, and efficacies. Extensive standardization is required to achieve consistency, composition, manufacturing process efficacy, and quality. The phytochemicals need rigorous and detailed clinical trials to reach international standards for developing medicinal compositions. Studying the plant metabolites and probiotics for their anti-cancer properties can get complicated due to the herb investigated, the biochemical tool used, and the study system adopted. A plant metabolite cannot give desirable results in all the combinations, limiting the study [135].

9. Conclusions

As plant-derived bioactive compounds have been used as natural remedies against different types of disease and cancer, much more stringent control and regulation should be in place for the benefit of humanity. Several plant bioactive compounds such as polyphenols, flavonoids, alkaloids, caffeic acid, saponins, polysaccharides, glycosides, triterpenoids, and glycosides exhibit anti-carcinogenic properties. These include inhibitory effects on cancer cell proliferation, angiogenesis, and inflammation and inducing apoptosis against colon cancer. These compounds' primary function is to block tumor cell proliferation and initiate apoptosis via different pathways. Using these compounds from medicinal plants is an effective alternative to preventing and treating colon cancer. However, more highly controlled clinical trials are required before these can be used in treating colon cancer. These processes include getting herbal compounds in purified form to test their effectiveness against cancer cells in in vitro and in vivo models. Still, there are some issues regarding exploring leading validated phytochemical compounds for use in cancer. It is a complex process requiring more advanced analytical and technological methods for identifying potential compounds, their bioavailability and target tissue action. There are still several limitations to be addressed before approving any of these compounds for regular use in treating colon cancer.

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CRediT authorship contribution statement

The authors confirm contributions to the paper as follows: Conceptualization, design, drafting of the article, and data analysis done by AE;

data collection and review outline fulfilled by DV, SP, and UMZ. Critical revision and final approval of the version to be published by SA, SP and AKDR. In addition, all authors have reviewed the conclusion and final version of the manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

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