

Review of the Anti-Cancer Potential of *Mirabilis Jalapa* and *Borago Officinalis* Leaves: Protection against Colorectal Cancer

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Abstract

Colorectal cancer (CRC) is a major cause of cancer morbidity and mortality, and there is an urgent need for safer and mechanistically distinct therapeutic approaches. This review critically analyses the anticancer potential of *Mirabilis jalapa* and *Borago officinalis* with focus on their phytochemical composition, molecular targets, experimental evidence, safety concerns, and translational potential. Constituents reported from these species can modulate oxidative stress, inflammation, apoptosis, cell-cycle progression, angiogenesis, epigenetic regulation, cancer stem cell persistence, and signalling in the tumour microenvironment. *Mirabilis jalapa* contains ribosome-inactivating proteins and phenolics of diverse nature with direct cytotoxic potential. *Borago officinalis* contains polyphenols, fatty acids and other bioactives associated mainly with antioxidant and anti-inflammatory effects. However, the evidence to date is dominated by in vitro studies, indirect mechanistic extrapolation and incompletely standardised extracts. Therefore, robust organoid and animal studies for colorectal cancer, pharmacokinetic characterisation, toxicological evaluation and formulation optimisation are required. These botanicals are promising platforms for drug discovery, however, clinical development requires stringent validation, standardisation and biomarker-guided studies within the framework of modern precision oncology.

Key words: Colorectal cancer, *Borago Officinalis*, *Mirabilis Jalapa*.

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Introduction

Colorectal cancer is a major public health issue globally, as it is one of the most frequently diagnosed cancers and a leading cause of cancer-related mortality [1]. A recent meta-analysis of 9,278 pr CRC survivors shows alarming rates of malnutrition - 12.10% mild, 33.13% moderate and 47.78% overall, with especially high rates reported in Asian populations and low to middle income countries [2]. Demographic, clinical and lifestyle determinants such as male sex, advanced tumour staging, metastatic spread, cancer therapies, smoking, alcohol consumption and comorbid metabolic diseases are further impacting such nutritional deficiencies.

The intestinal microenvironment is another level of complexity. Persistent inflammatory signalling, oxidative stress, altered epithelial barrier function and dysbiosis can act in concert with genetically initiated epithelial clones to sustain proliferative and survival programs. Regulatory nodes connecting NF- κ B, STAT3, Wnt/ β -catenin, PI3K/AKT/mTOR and MAPK signalling pathways mediate the effects of cytokines, growth factors and redox disturbances on cell-cycle progression, apoptosis, angiogenesis and invasion. Epigenetic mechanisms (such as DNA methylation, histone modifications and non-coding RNA networks) further stabilise malignant phenotypes and contribute to heterogeneity between patients [13-16]. This mechanistic complexity provides a strong rationale for testing multi-target natural products,

provided that claims of efficacy are linked to experimentally demonstrated targets rather than solely to antioxidant capacity.

CRC is a biologically heterogeneous disease and not a single molecular entity. The evolution of the tumour is a mirror of the sequential interplay of chromosomal instability, microsatellite instability, CpG-island methylation, oncogenic driver mutations and the remodelling of the immune and stromal microenvironment. These alterations control the rate of progression from adenoma to carcinoma, but also metastatic competence and therapeutic sensitivity. Molecular stratification is therefore of increasing clinical relevance, especially in identifying mismatch-repair deficient or microsatellite instability-high tumours and in interpreting alterations in RAS, BRAF and other actionable pathways. Symptoms are still stage-dependent and can be nonspecific, leading to delayed diagnosis in some patients, thus screening, molecular characterisation and risk-adapted management remain central elements of disease control [10-12].

CRC Results from malignant transformation of epithelial cells lining the colon or rectum, typically progressing through a well- characterised adenoma carcinoma sequence shaped by environmental inserts and cumulative genetic perturbation [3] as shown in figure 1. Mutational landscapes have led to the classification of CRCs into hypermutated and non-hypermutated phenotypes with abbreviations in canonical genes such as TP53, APC, KRAS,

NRAS and BRAF Playing pivotal role in humoral initiations and therapeutic resistance [4,8]. Clinically common manifestations include a matter alerted bound function involuntary weight loss and systemic fatigue [5]. At the molecular scale, dysregulation of critical pathways including Wnt/ β -catenin, PI3K/Akt/m.

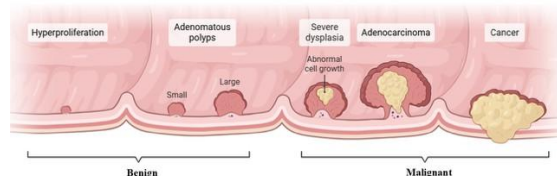


Figure 1. Benign-to-malignant transformation of colorectal epithelium across the adenoma-carcinoma sequence.

Phytochemicals in the Prevention and Treatment of Colorectal Cancer: TOR, MAPK and TGF- β Promote Tumour Progression, Metastasis, and Immune Evasion [6,7]. An increasing number of non-coding RNAs (miRNAs, lncRNAs, circRNAs) are acknowledged as epigenetic regulators of these oncogenic cascades [9]. Chemotherapeutic agents such as irinotecan, oxaliplatin, 5-fluorouracil, capecitabine, and trifluridine/tipiracil remain the mainstay of treatment [17]. However, their clinical application is often limited by narrow therapeutic indices, cumulative toxicity, multidrug resistance, and high economic burden [18–21]. The limitations have spurred and accelerated the search for plant-derived therapeutic agents that can synergise with or replace conventional chemotherapies. Phytoconstituents with their multi-target action and relatively favourable toxicity profiles represent a promising frontier in CRC drug discovery [13–16].

2. Role of Phytochemicals in Colorectal Cancer Prevention and Treatment

Phytochemicals are bioactive secondary metabolites broadly distributed in medicinal and dietary plants and have gained prominence as attractive candidates for CRC prevention and therapeutic intervention owing to their pleiotropic biological activities and capacity to modulate multiple molecular targets simultaneously. Phytochemicals have been reported to have anticancer properties, including polyphenols, flavonoids, phenolic acids, terpenoids, alkaloids, organosulfur compounds, and anthocyanins, by modulating the major processes involved in CRC initiation and progression, such as uncontrolled cell proliferation, apoptosis resistance, oxidative stress, chronic inflammation, angiogenesis, invasion, metastasis, epithelial–mesenchymal transition (EMT), and oncogenic signalling [22] as shown in **Figure 2**.

Figure 2. Principal phytoconstituent classes reported in *Mirabilis jalapa* and *Borago officinalis* and their proposed relevance to colorectal cancer prevention and therapy.

Several phytochemicals (**Table 1**) can also modulate the tumour microenvironment, intestinal microbiota and cancer stem-cell populations, therefore conferring a more general chemopreventive and therapeutic effect. Among the most studied phytochemicals, curcumin, resveratrol and sulforaphane have manifested various mechanisms against CRC. Curcumin suppresses CRC progression by modulating Wnt/ β -catenin, NF- κ B, PI3K/AKT and MAPK pathways and by enhancing apoptosis, cell-cycle arrest and inhibitory effects on inflammatory and angiogenic signalling. Resveratrol has been reported to suppress proliferation, migration, inflammation and tumour survival by modulating Wnt/ β -catenin, PI3K/AKT, NF- κ B and MAPK signalling. Sulforaphane is an isothiocyanate from cruciferous vegetables and is known as a promoter of phase-II detoxification pathways and has been associated with HDAC inhibition, cell-cycle arrest, apoptosis and modulation of Wnt/ β -catenin signalling [23,24]. Other phytochemicals that have been shown to exert anti-proliferative, pro-apoptotic and anti-inflammatory activities in a variety of CRC models include quercetin, anthocyanins, EGCG, lycopene and apigenin. For example, quercetin can influence MAPK, NF- κ B, PI3K/AKT, and Wnt/ β -catenin signalling, and EGCG has been associated with β -catenin degradation and inhibition of CRC cell proliferation. Apigenin can inhibit nuclear accumulation of β -catenin to suppress proliferation, migration and invasion of CRC cells. Significantly, the anticancer potential of phytochemicals is not limited to direct cytotoxicity. Their ability to restore the balance between pro- and anti-apoptotic proteins, regulate reactive oxygen species (ROS), inhibit inflammatory mediators such as NF- κ B and COX-2, inhibit angiogenic factors such as VEGF, and disrupt EMT and cancer stem-cell properties suggests a multi-level approach to CRC management. This multitarget behaviour might be of particular benefit against CRC, where concomitant dysregulation of several signalling networks contribute to tumour initiation, progression and therapeutic resistance [25].

3. Molecular Mechanisms Underlying Phytochemical-Mediated Colorectal Cancer Suppression

Dietary and plant-derived phytochemicals exert anticancer effects in CRC through mechanisms beyond simple cytotoxicity and involve coordinated regulation of proliferative, inflammatory, oxidative, angiogenic, apoptotic and epigenetic networks. Inhibition of Notch, Wnt, PI3K/Akt, NF- κ B and AP-1 signalling can restrict uncontrolled proliferation, while regulation of p53, p21, Bcl-2-family proteins, cytochrome c and caspases induces cell-cycle arrest and program cell death. Simultaneously, interference of EGFR/VEGFR/PDGFR associated signalling and

inflammatory mediators may inhibit angiogenesis and signalling for tumour support. Modulation of DNMT, HDAC and HAT activity provides an epigenetic level of control. **Figure. 3** shows these interconnected actions and provides light on the growing interest in phytochemicals as multi-target candidates for CRC chemoprevention and adjunctive therapy [54].

Figure 3. Major molecular mechanisms by which diet-derived phytochemicals may suppress colorectal cancer progression through regulation of cell proliferation, angiogenesis, oxidative stress, and epigenetic processes.

Mechanistically, the best-characterized CRC-directed phytochemicals exemplify why pathway-level interpretation is more informative than simple classification by chemical family. Curcumin suppresses proliferative and inflammatory signalling and induces mitochondrial and receptor-mediated apoptosis. Quercetin modulates PI3K/AKT, MAPK, and Wnt-related responses. Resveratrol inhibits invasion, survival, and β -catenin-dependent transcription. EGCG might modulate Notch and β -catenin signalling. Sulforaphane activates Nrf2-related stress responses and epigenetic regulation. Lycopene has been associated with the inhibition of AKT-dependent growth. Apigenin may restrict proliferation and metastatic behaviour [26-34]. Although these compounds are not unique to *M. jalapa* or *B. officinalis*, they provide a mechanistic benchmark against which less extensively characterised botanical extracts should be evaluated. The central translational question is thus not if an extract contains antioxidant or phenolic constituents, but whether chemically defined components reach biologically relevant concentrations, modulate validated CRC targets and reproduce activity in models that approximate human disease.

Table 1. Mechanistic landscape of major phytochemicals targeting colorectal cancer hallmarks and signaling pathways.

CR Hallmark / process	Representative phytochemical(s)	Principal molecular nodes	Expected biological readout	Potential translational significance	Ref.
Sustained	Curcumin; apigenin	Wnt/ β -catenin	Reduced proliferation;	Supports multi-	[25, 34, 5]

proliferation / cell-cycle progression	in	n; PI3K/AKT; MAPK; cyclin - associated signalling	cell-cycle arrest	node suppression of proliferative signalling rather than single-target cytotoxicity	
Resistance to apoptosis	Curcumin; sulforaphane	Bax/Bcl-2 balance; caspases; p53; mitochondrial and death-receptor pathways	Cytochrome-c/caspase activation; apoptotic cell death	Provides mechanistic endpoints for validating pro-apoptotic activity in CRC models	[25, 30, 31, 55]
Tumour-promoting inflammation	Curcumin; quercetin; resveratrol	NF- κ B; COX-2; MAPK;	Reduced inflammatory signalling and survival	Relevant to inflammation-driven	[25-27]

mm atio n		PI3K/ AKT	cues	CRC and potent ial adjun ctive chem oprev ention	
Inva sion / meta stasi s	Resve ratrol; apigen in	MAL AT1/ Wnt/ β - cateni n; MAP K; PI3K/ AKT	Reduced migratio n and invasion	Highli ghts metas tatic signal ing as a distin ct effica cy endpo int beyon d cell viabili ty	[27, 34]
Ang ioge nic sign alin g	EGC G; phyto chemi cal combi nation s	Notch - associ ated signal ing; VEG F- linked angio genic proces ses	Reduced prolifera tive/angi ogenic activity	Suppo rts evalu ation of vascul ar and tumou r- growt h endpo ints in advan	[28, 29]

				ced precli nical model s	
Oxi dati ve- stres s adap tatio n	Sulfor aphan e; lycope ne	Nrf2; Akt; redox- respo nsive signal ing	Altered ROS handling ; growth inhibitio n/apopto sis	Usefu l for linkin g redox modul ation to tumou r- selecti ve biolog ical respo nses	[30- 33]
Ther apy sens itiza tion / com bina tion resp onse	Curcu min; querce tin- contai ning nanof ormul ation	NF- κ B/Sr c; immu ne- and delive ry- associ ated mecha nisms	Enhance d anticanc er response in combina tion settings	Provi des a ration ale for testin g phyto chemi cals as adjuv ants rather than standa lone agents	[25, 26]

Curcumin is a representative example of this multi-target behaviour. Curcumin-induced apoptosis in

CRC models occurs via both intrinsic mitochondrial and extrinsic death-receptor pathways. Alterations in JNK/p38-p53 signalling, NF-κB and COX-2, PI3K/Akt, ROS homeostasis, Bcl-2-family proteins, DR5/Fas signalling, mitochondrial cytochrome-c release and downstream caspase activation have been reported. Curcumin can also modulate transcriptional regulators involved in proliferation and survival, linking apoptotic signalling to cell-cycle regulation. The integrated mechanism is shown in **Figure 4** and supports the broader concept that phytochemicals can act simultaneously at several dysregulated nodes in CRC [25,55].

Figure 4. Integrated intrinsic and extrinsic mechanisms implicated in curcumin-mediated apoptosis and cell-cycle regulation in colorectal cancer.

4. *Mirabilis jalapa* (Four O'clock Plant)

Mirabilis Jalapa has been shown to possess a wide range of pharmacological effects, particularly those that are mediated by cytotoxic proteins and ribosome-inactivating proteins (MAPs) that can induce apoptotic death in and cancer cell lines, including HCT 166 CRC cells [35-44]. Add phytochemical landscape rich in flavonoids, aikinites, saponins, tannins, glycosides with anti-microbial, anti-inflammatory and anti-tumour properties. GC-MS profiling indicates abundance of active compounds [37-42]-confers antioxidants, anti-microbial, anti-inflammatory, anti-tumour properties [38,43,45]. GC-MS profiling reveals that plants are rich in bioactive compounds like 9-octadecenamide and possess anti-proliferative activity along with redox modulation [42]. These properties make am Jalapa a very promising botanical candidate for further translational oncology research.

5. *Borago officinalis* (Borage)

Borago officinalis, an Anthro Medically valued herbal enriched in Gamma Linolenic acid (GLA), possesses well-documented antioxidants, anti-inflammatory, hepatoprotective and anti-microbial properties [46-49]. Its diverse phytochemical profile, including phenolic acids, flavonoids, alkaloids, and terpenoids, further contributes to its broad therapeutic potential [50]. Comparative studies have reported that wild-type populations may possess higher phenolic content and stronger antioxidant activity than cultivated varieties, highlighting the influence of plant origin and cultivation conditions on phytochemical composition and biological activity [51]. Extract of *B. Officials* exhibit marked anti-genotoxic and cytotoxic effects attributable largely to resuming asset and other phenolic constituents. Importantly, these findings suggest that *B. officinalis* may exert anticancer effects through multiple complementary mechanisms, including modulation of oxidative stress, inhibition of

cellular proliferation, induction of apoptosis, and protection against genotoxic damage [52]. Recent advances in nanotechnology have further expanded the therapeutic potential of *B. officinalis*. Biosynthesized silver nanoparticles (AgNPs) using *B. officinalis* extracts have demonstrated enhanced anticancer activity, including selective cytotoxic effects against A549 and HeLa cell lines, suggesting that plant-mediated nanomaterials may improve the biological activity of its phytoconstituents. Such approaches may also provide opportunities to enhance bioavailability, cellular uptake, and targeted delivery of plant-derived bioactives. However, evidence specific to colorectal cancer remains comparatively limited, and further studies using CRC-specific cellular and in vivo models are required to establish its molecular mechanisms, therapeutic efficacy, safety, and translational potential [53].

Table 2. Comparative anticancer evidence and translational readiness of *Mirabilis jalapa* and *Borago officinalis* in colorectal cancer research.

Botanical candidate / evidence source	Reported anticancer supportive activity	Mechanistic relevance to CRC	Strength of current evidence	Key translational limitation	Ref.
<i>Mirabilis jalapa</i> – purified proteins / ribosome-inactivating proteins	Cytotoxic and apoptotic inducing activity reported in cancer cell models	Supports direct pro-apoptotic and anti-proliferative potential relevant to CRC	Mode of action: direct anticancer activity reported, but CRC-specific validation remains	Requires standardized extracts/proteins, CRC-specific models, dose-response studies and in	[35, 43]

			ns limite d	vivo confir mation	
<i>Mirabilis jalapa</i> – phytochemical and antioxidant evidence	Flavonoids, saponins, tannins, glycosides and other constituents show antioxidant, antimicrobial and anti-inflammatory activities	Redox and inflammatory modulation may complement direct anticancer mechanisms	Low–mode rate: largely supportive pharmacology rather than direct CRC evidence	Active constituents and molecular targets need isolation and mechanistic validation	[37–45]
<i>Borago officinalis</i> – phenolic/flavonoid-rich extracts	Antioxidant, anti-inflammatory, antiperoxidative, anticarcinogenic and cytotoxic activities	Potential modulation of oxidative stress, inflammation, proliferation	Mode rate supportive evidence; direct CRC evidence remains compelling	Needs CRC-specific cellular and animal studies and standardized phytochemicals	[46–52]

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<i>Borago officinalis</i> – plant-mediated silver nanoparticles	Enhanced anticancer activity and selective cytotoxicity reported in A549 and HeLa cells	Illustrates potential of nanotechnology to improve delivery and biological activity of plant-derived constituents	Preclinical and indirect for CRC	CRC-specific efficacy, safety, pharmacokinetics and formulation reproducibility remain unestablished	[53]
Comparative translational perspective	Both plants provide multi-component, multi-target pharmacological profiles	Potential convergence on apoptosis, oxidative stress and inflammatory signaling	Preclinical / hypothesis-generating	Lack of standardized formulations, robust CRC-specific in vivo evidence and clinical validation	[35–53]

6. Synergistic Potential with Conventional Colorectal Cancer Therapy

The therapeutic importance of plant-derived bioactives in colorectal cancer is not limited to their direct cytotoxic effects, but also includes their potential use as chemosensitizing and treatment supportive agents. Conventional management of CRC is focused on 5-fluorouracil, oxaliplatin and irinotecan based regimens, however acquired resistance, cumulative toxicity and activation of compensatory survival pathways often limit durable responses. Besides these agents, phytochemicals can synergistically inhibit the signalling pathways of NF- κ B, PI3K/AKT/mTOR, MAPK and Wnt/ β -catenin, induce pro-apoptotic responses, and decrease oxidative and inflammatory stress. Larger phytochemical studies on CRC indicate that the selected natural compounds can potentiate tumour suppression related to chemotherapy and, in some cases, potentiate the response to treatment, but these data cannot be directly extrapolated to *Mirabilis jalapa* or *Borago officinalis* due to the lack of combination studies involving these two species [54,55]. This distinction is important for the translational interpretation of the present review. The phytochemical diversity of *M. jalapa* and *B. officinalis* offers a mechanistic rationale for investigating combination strategies particularly where their constituents converge on apoptosis, redox homeostasis, inflammatory signalling and proliferative control. However, before claiming synergy, future studies should establish combination indices, dose-response relationships and pharmacodynamic interactions with standard CRC drugs. The experiments should include resistant CRC cell lines, 3D tumour models and in vivo systems followed by assessment of tumour burden, apoptosis, oxidative injury and pathway-specific biomarkers. Special attention should also be paid to pharmacokinetic interactions, as phytochemicals may modify the activity of cytochrome P450 enzymes or drug transporters, thereby affecting the exposure to conventional anticancer agents [56]. The most defensible contemporary position is that these botanicals are candidates for mechanistically directed adjuvant investigation and not established adjuncts to CRC chemotherapy.

7. Evidence Hierarchy and Translational Interpretation

A critical appraisal of phytochemical research needs to clearly differentiate between mechanistic plausibility and therapeutic evidence. Cell line studies are essential to establish concentration response relationships and molecular targets, but often use exposures that are not easily recapitulated systemically. Animal models are of higher biological integration but differences in metabolism, microbiota, tumour induction and

dosing may limit direct extrapolation to patients. Thus, human data are critical and systematic reviews of polyphenols in CRC continue to reveal a large discrepancy between promising preclinical findings and consistent clinical benefit [59-61]. This gap is particularly relevant for curcumin, resveratrol and quercetin, where there is a large mechanistic literature, as well as pharmacokinetic limitations and heterogeneous clinical results [62-64].

Bioavailability is a common contributor to this translational gap. Many polyphenols are poorly soluble in aqueous solutions, unstable in the intestine, rapidly conjugated or extensively metabolised during first pass metabolism, leading to tissue exposures that may be much lower than concentrations used in vitro. Nanoformulation, lipid-based carriers, polymeric systems and other delivery approaches are being investigated to improve solubility, protect labile compounds and increase tumor-directed exposure [65-67]. Although scientifically appealing, these technologies should not be taken as evidence of clinical efficacy; formulation-dependent changes in biodistribution, toxicity, manufacturability and regulatory complexity also need to be demonstrated. Recent CRC nanomedicine research also suggests that oral systems interacting with the intestinal microenvironment may influence antitumor immunity and microbial metabolites, leading to the development of locally active phytochemical strategies [68].

8. Challenges and Research Gaps

Despite promising preclinical evidence, the clinical translation of phytochemical-based therapeutics for colorectal cancer (CRC) remains a challenge. A major limitation is the lack of robust CRC-specific cellular and animal models that adequately reflect tumour heterogeneity, microenvironment and metastatic behaviour, which can impede mechanistic interpretation and clinical predictability. Moreover, the slow translation of promising phytochemicals into well-designed human clinical trials hinders the validation of their safety, efficacy, pharmacokinetics, pharmacodynamics, and long-term therapeutic outcomes. Standardisation and Reproducibility are also major issues, as differences in plant cultivation, geographical origin, harvesting, extraction methods and phytochemical composition can have a substantial effect on biological activity and dose consistency. Additionally, many phytochemicals are poorly soluble, bioavailable, rapidly metabolised, and systemically retained for only short durations, which limits their therapeutic exposure. However, such limitations can be overcome by advanced delivery approaches like nanoparticles, liposomes, phytosomes and micelles but further investigation is needed in the areas of formulation optimisation, scalability, stability and

regulatory acceptance. Another important aspect is safety, particularly with long-term or high-dose use and potential herb-drug interactions with conventional anticancer treatments. Therefore, extensive toxicological and pharmacokinetic and pharmacodynamic studies are necessary to determine appropriate therapeutic windows. Finally, regulatory uncertainties related to complex botanical preparations and quality control requirements continue to hinder commercialisation. Addressing these interrelated challenges through standardised formulations, CRC-relevant models, rigorous clinical validation, advanced delivery technologies, and multidisciplinary collaboration will be critical for translating promising phytochemicals into safe and clinically effective CRC therapeutics.

9. Safety, Toxicological Considerations and Clinical Translation

The translation of botanical anticancer candidates requires safety evaluation with the same rigour as pharmacological efficacy. Variability in plant part, geographical origin, cultivation conditions, extraction solvent and phytochemical composition can result in substantial differences in biological activity and toxicological profile for *M. jalapa* and *B. officinalis*. Thus the extract should be standardised prior to further advanced efficacy studies and should involve botanical authentication, quantitative chemical fingerprinting, specification of marker compounds and assessment of contaminants. Studies of repeated-dose toxicity, genotoxicity, hepatic and renal safety, reproductive toxicity where appropriate, and pharmacokinetic characterisation must be conducted prior to proposing clinically meaningful dose ranges. These requirements are particularly valid for botanical preparations intended for long-term use or in conjunction with cytotoxic therapy.

B. officinalis warrants further study as the Boraginaceae family has been shown to contain unsaturated pyrrolizidine alkaloids, compounds of genotoxic and hepatotoxic concern. The available literature does not support the assumption of an equivalent risk profile for all borage preparations. Risk is dependent on plant material, chemical composition, processing and exposure. Thus, in future anticancer development, chemically characterised preparations with explicit pyrrolizidine-alkaloid assessment and, if possible, PA-depleted or otherwise safety qualified extracts should preferably be used [57,58]. Herb-drug interactions are a second translational concern as modulation of CYP enzymes and membrane transporters could alter the disposition of co-administered anticancer agents [56]. These considerations further emphasise the need to move from descriptive phytochemical screening to standardised products with toxicokinetic data, clinically relevant exposure levels and

predetermined quality specifications. Currently, the evidence base for direct CRC treatment with *M. jalapa* and *B. officinalis* is largely preclinical and much less developed than that for extensively studied phytochemicals such as curcumin, quercetin and resveratrol. Therefore clinical translation should be achieved in a phased manner: validation of CRC specific activity in reproducible models; identification of active constituents and molecular targets; pharmacokinetic and toxicological qualification; assessment of rational combinations with standard therapy; and finally well designed early phase clinical studies. This sequence would differentiate true therapeutic potential from non-specific antioxidant or cytotoxic effects and provide the evidence necessary to determine whether either botanical can progress from ethnopharmacological interest to a standardised CRC-directed intervention.

10. Emerging Mechanistic and Formulation Priorities

Future development should focus on biomarker-defined hypotheses that are experimentally testable rather than broad claims of antioxidant activity. Cancer stem-cell populations are particularly relevant, involved in recurrence, metastatic dissemination and resistance. Several nutraceuticals have been investigated as modulators of stemness-associated signalling, including curcumin, EGCG, sulforaphane, resveratrol and genistein [69,70]. Epigenetic regulation is a complementary approach. Natural compounds can modulate the expression of the genes involved in proliferation, apoptosis and drug response by affecting DNA methylation, histone acetylation and non-coding RNA networks [71,72]. These mechanisms are hypotheses for *M. jalapa* and *B. officinalis*, until verified by chemically characterised preparations, target-specific assays and suitable CRC models.

Equally important may be formulation science. Improved analyses of nanoformulated phytochemicals show increased apparent solubility, stability, cellular uptake and pharmacokinetic behaviour, particularly for resveratrol, quercetin and other poorly bioavailable polyphenols [73-75]. Natural polysaccharides are also being investigated to modify the intestinal microbial ecology, which may play a role in CRC prevention and immunological control [76]. However, the formulation itself can modify biological behaviour and therefore, particle size, surface chemistry, release kinetics, intestinal residence, and interaction with mucus should be considered as mechanistic variables and not simply as pharmaceutical parameters.

The botanical evidence base must also demand species-specific restraint. Ribosome inactivating proteins obtained from *M. jalapa* have shown cytotoxic potential and been investigated in

targeted nanoparticle systems, but much of the work has used non-CRC cancer models [77,78]. These results are consistent with biological activity of the protein fraction but do not establish colorectal efficacy. *B. officinalis* has been reported to have antigenotoxic and cytotoxic effects which are partly attributed to its phenolic composition, but recent reviews have pointed out that there is a large variation depending on the plant part, extraction method and phytochemical profile [79,80]. These observations emphasise the primary finding of this review: both plants are scientifically interesting sources of bioactive molecules, but the advancement toward CRC therapy needs a direct validation on the specific disease, rather than an extrapolation from the general anticancer activity.

11. Future Directions

Future studies should be focused on CRC-specific in vivo models to systematically understand the pharmacodynamic effects, therapeutic windows, pharmacokinetic profiles and systemic behaviour of plant-derived compounds [81,82]. Special emphasis should be given to their bioavailability, stability and site-specific delivery using nanotechnology-based drug delivery methods that can improve therapeutic efficacy and minimise off-target effects [83-85]. The advancement of these compounds toward clinical translation will necessitate the creation of standardised phytopharmaceutical formulations based on strict quality control, reproducible phytochemical profiling, dose optimisation, and comprehensive safety evaluation. Moreover, collaboration between ethnobotanists, pharmacologists, oncologists, formulation scientists, toxicologists, and regulatory authorities will be crucial for the integration of traditional knowledge with mechanistic evidence and modern paradigms of drug development. Overall, these collaborative initiatives may expedite the journey of potentially useful plant-derived compounds from the bench to well-characterized, evidence-based therapeutic candidates for CRC management.

12. Critical Synthesis and Research Priorities

The overall literature available indicates a multi-level framework for the interpretation of the anticancer potential of *M. jalapa* and *B. officinalis*. At the chemical level, both species contain classes of metabolites known to have redox, inflammatory and cytotoxic activities. At the cellular level, related phytochemicals can modulate apoptosis, cell-cycle progression, angiogenesis and signalling networks central to CRC biology. But at the whole organism level, the evidence is increasingly incomplete, especially when focus is limited to chemically standardised preparations of these two plants. This gradient of evidence is important because biological plausibility cannot replace demonstration of efficacy in CRC-specific models. Therefore, further studies should be initiated with authenticated plant material and reproducible

extraction followed by chromatographic or spectrometric fingerprinting, quantitative marker analysis and bioactivity-guided fractionation. Active fractions should then be tested in several CRC cell lines representing different molecular backgrounds rather than a single tumour model. Selectivity should be defined using normal colon epithelial cells and mechanistic claims should be supported using pathway-specific assays rather than inferred from changes in cell viability alone. A second priority is the use of models that better recapitulate tumour architecture and microenvironmental complexity. To determine whether activity seen in standard monolayer cultures translates to the presence of extracellular matrix, stromal cells and diffusion barriers, three-dimensional spheroids, patient-derived organoids and co-culture systems can be used [86,87]. In vivo experiments should include pharmacokinetic measurements to relate tumour responses to actual exposure to defined constituents. Local colonic concentrations, intestinal metabolism and microbiota mediated biotransformation may be as important as systemic plasma exposure for products administered orally. This is particularly the case for polyphenols and other phytochemicals that are rapidly metabolised, where low circulating concentrations do not imply a lack of activity in the gastrointestinal tract [88,89]. By contrast, therapeutic claims should not be based on high in vitro concentrations that cannot be achieved in the colon or circulation. Finally, translational development should be optimised for efficacy, safety and pharmaceutical feasibility at the earliest stage possible. Extracts with reproducible CRC-selective activity should then be subjected to dose-range toxicology, genotoxicity assessment, interaction studies with standard chemotherapeutics and assessment of formulation stability. In case of preparations being intended for repeated exposure, a chemical control of pyrrolizidine alkaloids is essential for *B. officinalis* [90]. Proteinaceous ribosome-inactivating components for *M. jalapa* may need delivery strategies that maintain activity while minimising nonspecific toxicity and immunogenicity. Nanocarriers are one way to improve stability, or localisation, but the added complexity needs to be justified by demonstrable gains in therapeutic index [91]. Ultimately, the best future studies will be those that link a defined botanical preparation to a measurable molecular target, a reproducible antitumor phenotype, an achievable exposure, and an acceptable safety margin. Such a chain of evidence would significantly bolster the case for these plants as sources of CRC-directed lead compounds and would move the field from descriptive phytochemistry to mechanism-informed translational pharmacology.

13. Conclusion

Biologically plausible but poorly validated sources of lead compounds directed against colorectal cancer include *Mirabilis jalapa* and *Borago officinalis*. Their phytochemical repertoires may interfere with interconnected determinants of tumour initiation and progression including oxidative and inflammatory signalling, dysregulated proliferation, apoptosis resistance, angiogenesis, epigenetic remodelling, cancer stem-cell maintenance, and treatment resistance. The strongest evidence is for general mechanistic relevance of constituent classes and for selected cytotoxic proteins from *M. jalapa*; direct colorectal cancer evidence for standardised preparations of either species is limited. Therefore, antioxidant activity or cytotoxicity in isolated cell systems should not be considered as evidence of therapeutic efficacy. The progress now relies on authenticated plant material, chemically characterised extracts, activity-guided fractionation, reproducible testing in colorectal cancer cell lines, patient-derived organoids and immunocompetent animal models. Besides efficacy, pharmacokinetic exposure, metabolism, tumour selectivity, herb-drug interactions and dose-dependent toxicity should be evaluated, particularly in view of the hepatotoxic pyrrolizidine alkaloids potentially present in *B. officinalis*. Nanocarrier and targeted-delivery platforms have the potential to increase stability, bioavailability and tumour accumulation but require separate safety assessment. Ultimately, the comparison of these botanicals with established therapies guided by biomarkers and carefully designed combination studies will determine if they can move from promising pharmacological resources to standardised and clinically credible interventions for prevention or treatment of colorectal cancer in future practice.

Author Contributions

Vikramjeet Singh: Conceptualisation, literature review, data compilation, writing, revision

Ravinesh Mishra: Supervision, critical review, editing and final approval

Bhartendu Sharma: Co-supervision, scientific guidance, review

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Conflict of Interest Statement

No conflict of interest

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