Retaining our Voice in a World of Co-regulation

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As the *CANDJ* team travelled to the Nova Scotia professional conference in October, we heard encouraging news from their provincial association annual meeting: naturopathic medicine will be a fully regulated Health Profession there by mid-2026, in an amalgamated College with the Nova Scotia College of Chiropractors (NSCC). Once this transition is achieved, it will bring the number of Canadian jurisdictions where naturopathic doctors are fully regulated to seven, well over half of the provinces and territories within Canada.

After what seems like several years of stalled regulatory expansion, this is a very positive step forward, and a collaborative model that makes sense for smaller provinces and territories where the naturopathic profession may have limited resources to create regulations and bylaws from the ground up.

Nova Scotia will actually be the second province to embrace co-regulation of regulated healthcare professions, after the amalgamation of the College of Naturopathic Physicians of BC (CNPBC) with the colleges of chiropractors, registered massage therapists, and traditional Chinese medicine practitioners and acupuncturists to create a new College of Complementary Health Professionals of BC (CCHPBC). While co-regulation offers efficiencies that ultimately help smaller healthcare professions like ours, it is important to underscore the importance of ensuring that each profession retains a strong voice and representation within any amalgamated structure. On the other hand, with each increase in the number of regulated provinces, it becomes easier to maintain forward momentum on regulatory expansion, as provincial Ministries of Health see the advantages of safely regulated naturopathic medicine to help fill the acknowledged and growing gaps in primary care delivery across Canada.

Globally, there are several advantages to professional regulation. Not only does it strengthen public confidence by providing appropriate oversight and title protection, it also allows room for the profession to grow and innovate. Additionally, it increases opportunities for interprofessional learning and collaboration, which the national team Primary Care Project has been proposing for several years.

Increasing the number of regulated provinces will also strengthen the foundation for greater alignment in scope and recognition across Canada, creating more opportunities for naturopathic doctors to contribute fully to primary care and service delivery, particularly in underserved areas.

This edition leads off with two reviews: one on integrative strategies for managing endometriosis, by Kolomitseva, and the second from an international team exploring recent findings on the interaction of the gastrointestinal (GI) microbiome and cancer. The Kolomitseva review synthesizes recent literature on a range of integrative and naturopathic therapeutics for endometriosis, with a systematic and critical approach that addresses a known gap in the literature, and makes the case for inclusion of well-supported therapies in interdisciplinary frameworks. The second review, by Barry et al., is the first in a two-part series the authors have in development. The one we are publishing in this edition focuses on the state of current knowledge of the role of the microbiome in the formation and treatment of cancers, centring on conventional therapeutics.

Our commentary in this issue is a broad-ranging narrative from Iva Lloyd, previously the President and currently the CEO of the World Naturopathic Federation, about the evolution of the World Health Organization's engagement with traditional medicine (TM) since the 1970s. As someone who has had a ringside seat for much of the evolution of the WHO's approach to TM (which includes naturopathic medicine and naturopathy), she outlines current progress but also challenges that could impact the naturopathic profession. One of the issues she discusses is a series of changes by the WHO to the nomenclature and definition of terms within traditional and complementary medicine over the last decade, which have resulted in confusion for both peer-reviewed publications such as ours, and also for the many researchers and authors trying to keep abreast of current naming standards. Instead of the current standard WHO language of traditional, complementary, and integrative medicine or TCIM, she proposes a change to TICIM (traditional, Indigenous, complementary, and integrative medicine) to distinguish systems of medicine from practice or assessment tools.

Since our transition at *CANDJ* to open access format in June, our editorial team has noticed a definite uptick in submissions,

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Integrative Strategies for Managing Endometriosis—A Comprehensive Narrative Review

Anna Kolomitseva,[1] ND

ABSTRACT

Endometriosis is a chronic, estrogen-dependent inflammatory disorder affecting 10–15% of women of reproductive age. It contributes to chronic pelvic pain, infertility, and diminished quality of life. While conventional therapies—including hormonal agents, NSAIDs, and surgery—can offer symptom relief, recurrence remains high, prompting many patients to explore integrative and naturopathic approaches.

This narrative review synthesizes findings from 27 clinical studies—including randomized controlled trials, systematic reviews, and meta-analyses—evaluating dietary, nutraceutical, botanical, acupuncture, and lifestyle interventions for endometriosis management.

Anti-inflammatory dietary patterns such as the Mediterranean and low-FODMAP diets were associated with reduced pain and inflammation. Nutraceuticals, including omega-3 fatty acids, curcumin, resveratrol, and vitamins C, D, and E, showed potential to alleviate pelvic pain and oxidative stress. Acupuncture and Chinese herbal medicine demonstrated benefits in symptom reduction and quality of life. Mind–body therapies such as yoga and multimodal self-management programs improved psychological well-being and coping.

Collectively, these modalities offer low-risk, mechanism-based adjuncts that can be integrated into patient-centred care while large phenotype-stratified trials are conducted.

Key Words Naturopathic medicine, botanical medicine, integrative therapies, inflammation, diet, acupuncture, women's health

INTRODUCTION

Background

Endometriosis is a chronic, estrogen-dependent inflammatory disorder defined by the ectopic presence of endometrial-like tissue outside the uterine cavity, most commonly affecting the ovaries, fallopian tubes, and pelvic peritoneum. The global prevalence is estimated at approximately 10–15% of reproductive-aged women, though diagnostic delays and under-recognition may understate this figure.[1]

Clinically, the condition presents with a constellation of symptoms including chronic pelvic pain, dysmenorrhea, dyspareunia, fatigue, gastrointestinal symptoms (e.g., bloating, constipation), and infertility—factors that significantly impair quality of life, mental health, and work productivity.[2]

The underlying pathophysiology is multifactorial, involving chronic systemic and local inflammation, hormonal imbalances (particularly estrogen dominance), progesterone resistance, and immune dysregulation. These processes foster aberrant angiogenesis, oxidative stress, and persistent activation of macrophages, which sustain the inflammatory milieu and pain sensitization in the endometriotic niche.[3]

Emerging molecular and immunological data suggest an interplay between inflammatory cytokines (e.g., IL-6, TNF-α), oxidative damage, and endocrine-immune crosstalk, contributing to lesion persistence and therapeutic resistance. Endometriosis has thus increasingly been conceptualized not solely as a gynecological disorder, but as a chronic systemic condition with far-reaching metabolic and immunologic implications.[3,4]

Current Standard of Care and Limitations

The current conventional management of endometriosis centers on hormonal suppression and surgical removal of ectopic endometrial tissue. First-line pharmacologic treatments include combined oral contraceptives, progestins, and gonadotropin-releasing hormone (GnRH) agonists or antagonists, aimed at reducing

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estrogen-driven proliferation of ectopic lesions.[5] Nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used for pain control, though they do not address the underlying pathology.[6]

While these interventions can provide short-term symptom relief, they are often associated with significant limitations. Hormonal therapies may cause adverse effects such as breakthrough bleeding, weight gain, mood alterations, and decreased bone mineral density with prolonged use.[5] Additionally, suppression of ovulation is contraindicated in women actively trying to conceive.

Surgical excision, typically performed via laparoscopy, remains the gold standard for definitive diagnosis and removal of endometrial lesions. However, recurrence rates remain high—estimated at 21.5% within 2 years and up to 50% within 5 years postoperatively—necessitating repeated interventions in many cases.[7]

Collectively, these limitations underscore a therapeutic gap and the need for more sustainable, low-risk adjunctive options. This has prompted growing interest in integrative and naturopathic modalities that aim to reduce systematic inflammation, modulate immune dysfunction, and improve long-term symptom control through non-hormonal means.

Role of Naturopathic and Integrative Medicine

In response to the limitations of conventional treatments, a growing number of individuals with endometriosis are turning to integrative and naturopathic approaches to manage their symptoms and improve quality of life. These approaches emphasize individualized, patient-centred care that targets the multifactorial pathophysiology of endometriosis—including inflammation, oxidative stress, hormonal imbalance, and immune dysfunction—through a combination of dietary modifications, botanical therapies, nutraceuticals, acupuncture, and mind–body practices.[8,9]

Unlike pharmacological or surgical interventions that often provide short-term relief or carry significant side effects, naturopathic strategies are designed to support systematic balance and reduce symptom recurrence. For instance, botanical compounds such as curcumin and resveratrol exhibit anti-inflammatory and immunomodulatory properties, while nutritional interventions like the Mediterranean or low-FODMAP diets may influence hormonal metabolism and gastrointestinal symptoms.[10-12] Acupuncture and Traditional Chinese Medicine (TCM) approaches provide additional avenues for neuromodulation and pain control.[8,13]

Clinically, integrative therapies are increasingly used as adjuncts to conventional care, offering a more comprehensive and sustainable approach to symptom management. As evidence supporting these modalities grows, their inclusion in clinical guidelines and interdisciplinary care frameworks warrants serious consideration.

Previous Reviews and the Literature Gap

While several systematic reviews have assessed the efficacy of conventional treatments—such as hormonal therapies and laparoscopic surgery—for endometriosis, relatively few have focused on integrative and naturopathic modalities. The available literature on complementary approaches tends to evaluate individual interventions in isolation, such as dietary changes or specific supplements, without synthesizing evidence across domains. For example, a meta-analysis on dietary intake and endometriosis risk was undertaken, while another explored the effectiveness of dietary interventions, yet neither incorporated botanicals, acupuncture, or lifestyle therapies comprehensively.[14,15]

Additionally, many existing reviews lack rigorous evaluation of dosage ranges, mechanisms of action, or clinical endpoints such as recurrence rates, quality of life, or inflammatory biomarkers. This fragmented landscape makes it challenging for clinicians to implement evidence-based integrative strategies. As such, there remains a critical need for a comprehensive synthesis of clinical data on naturopathic interventions—including botanical medicines, nutraceuticals, acupuncture, and lifestyle practices—to support more informed, integrative clinical decision-making for endometriosis management.[14,15]

Objective and Structure of this Review

This narrative review aims to synthesize and critically evaluate current clinical evidence on naturopathic and integrative interventions for the management of endometriosis. Drawing from recent randomized controlled trials, systematic reviews, and meta-analyses published between 2020 and 2025, the review explores the efficacy and safety of interventions such as dietary modification, botanical and nutraceutical supplementation, acupuncture, and lifestyle therapies.

The discussion is structured thematically by intervention type, with emphasis on clinically meaningful outcomes, including symptom severity (e.g., pelvic pain, dysmenorrhea), inflammatory and oxidative stress biomarkers, hormonal profiles, quality of life, and recurrence risk. The goal is to provide clinicians and researchers with a comprehensive yet practical overview of integrative strategies that may serve as adjuncts or alternatives to conventional medical treatment.

METHODS

This narrative review employed a structured literature search to identify clinical studies evaluating integrative and naturopathic interventions for endometriosis.

Data Source and Search Strategy

The electronic databases PubMed, Science Direct, and Google Scholar were searched in July 2025 for relevant publications between January 2020 and May 2025. For Google Scholar, the search depth was limited to the first 100 results per query.

The search combined Medical Subject Headings (MeSH) and free-text terms using Boolean operators:

(endometriosis) AND (women OR female OR menstruating) AND (naturopathic OR herbal OR botanical OR supplement OR nutraceutical OR diet OR dietary OR lifestyle OR acupuncture OR integrative OR complementary) AND (clinical trial OR randomized controlled trial OR systematic review OR meta-analysis OR narrative review OR efficacy OR treatment OR management).

Eligibility Criteria

- Primary inclusion: human clinical studies published in English, including randomized controlled trials (RCTs), non-randomized controlled trials, case reports/series (when clinically informative), systematic reviews, meta-analyses, and narrative reviews addressing integrative/naturopathic interventions for diagnosed endometriosis.
- Secondary inclusion: selected preclinical (in vitro or animal) mechanistic studies and non-clinical reviews/commentaries were included only to support or cite proposed biological mechanisms when original laboratory evidence was required.

Exclusion Criteria

- Pre-2020 publications with the exception of mechanistic papers, which were retained when necessary to cite original experimental findings.
- Non-clinical commentaries, editorials, or letters without original data were generally excluded from the primary evidence pool but were considered selectively for contextual discussion or guideline citations.

Data Extraction and Synthesis

Titles and abstracts were screened for relevance by the author. Full texts of potentially eligible articles were reviewed in full. Key data were extracted on study design, sample size, intervention type, dosage (if applicable), outcomes, and main findings. A narrative synthesis was conducted to summarize and integrate the evidence across intervention categories.

Thematic Categorization

Studies were grouped into the following domains for synthesis and discussion:

1. Dietary interventions
2. Botanical and nutraceutical interventions
3. Acupuncture and TCM
4. Lifestyle and mind–body therapies

RESULTS

Dietary Interventions

Numerous studies summarized in a review suggest that adherence to the Mediterranean diet may reduce endometriosis-associated symptoms, including pain and inflammation. The diet's richness in omega-3 fatty acids, antioxidants, and phytonutrients is believed to modulate prostaglandin synthesis and inflammatory pathways, potentially accounting for its therapeutic effects.[2] See Table 1 for a summary of key studies evaluating dietary interventions in endometriosis.

Similarly, a RCT investigated a 28-day low-FODMAP diet in women with endometriosis and reported a statistically significant improvement in gastrointestinal symptoms and pain scores, suggesting that gut-directed nutritional interventions may offer symptom relief in women with endometriosis-associated irritable bowel syndrome (IBS).[12]

Dietary intake of cruciferous vegetables, specifically Brassica bioactives, may support estrogen metabolism and exert anti-inflammatory effects. In vitro and ex vivo analyses showed these compounds modulate cytokine activity within the endometriotic microenvironment, though human clinical trials remain limited.[3]

Proposed Mechanisms

- Modulation of inflammatory signaling pathways (e.g., cytokines, prostaglandins)[3,4,30]
- Antioxidant effects reducing oxidative stress[4,17,18,31]
- Regulation of estrogen metabolism via phytochemicals (e.g., indole-3-carbinol)[3,35]
- Gut–immune interaction and improved bowel function (in low-FODMAP dietary context)[12,21,24,41]

TABLE 1 Dietary Interventions in Endometriosis

Study (Author, Year)	Intervention	Population	Study Type	Key Clinical Outcomes
Abramiuk et al., 2024*	Dietary ingredients	Narrative scope	Narrative Review	↓ CRP, ↓ pain scores, improved antioxidant status
Varney et al., 2021*	Low-FODMAP diet	Women with endometriosis and GI symptoms	RCT (crossover)	↓ bloating, ↓ abdominal pain, improved global
García-Ibañez et al., 2020*	Brassica bioactives	In vitro & ex vivo models	Preclinical (in vitro/ex vivo)	↓ inflammatory cytokines and oxidative stress
Cirillo et al., 2023	Mediterranean diet	Women with endometriosis	Observational clinical study	Adherence linked to ↓ oxidative stress markers and ↓ pain scores
Arab et al., 2022	Various food groups	Women in observational cohorts	Systematic review & meta-analysis	↑ red meat = ↑ risk; ↑ fruits/vegetables = ↓ risk
Nirgianakis et al., 2022	Low-FODMAP, anti-inflammatory	Women with endometriosis	Systematic review	↓ pain
Abulughod et al., 2024	Nutritional interventions	Narrative scope	Narrative review	Summarized anti-inflammatory roles of nutrients/diets
Markowska et al., 2023	Various dietary components	Narrative scope	Narrative review	Identified triggers and modulators in disease course

Studies marked with an asterisk (*) were directly discussed in the manuscript text.
CRP: C-reactive protein; GI: gastrointestinal; RCTs: randomized controlled trials

Botanicals and Nutraceuticals

Botanical and nutraceutical interventions have been increasingly explored for their role in modulating inflammation, oxidative stress, and hormone regulation in endometriosis. Table 2 summarizes key clinical and preclinical studies of botanical and nutraceutical interventions relevant to endometriosis management. Among these, curcumin has shown promise in reducing proinflammatory cytokines and oxidative stress. A review of preclinical and clinical data in female reproductive disorders suggested that curcumin at doses of 500–1000 mg/day may reduce inflammatory cytokines and oxidative stress. While human trials in endometriosis are lacking, the proposed mechanisms—such as NF-κB and COX-2 inhibition—support its potential role in symptom management.[10]

Omega-3 fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have demonstrated anti-inflammatory effects relevant to endometriosis. In a randomized, placebo-controlled trial, 1000 mg/day of omega-3 acids was administered to adolescent girls and young women with endometriosis over six months. Although the reduction in pain scores was not statistically significant, the findings suggest a potential role for omega-3 acids in modulating inflammation and pelvic pain in this population.[16]

Resveratrol, a polyphenol abundant in red grapes and berries, has biologically plausible anti-inflammatory and antioxidant actions relevant to endometriosis. In a macrophage–endometriotic cell co-culture model, resveratrol and related stilbenes down-regulated pro-inflammatory mediators (e.g., IL-6, IL-1β, TNF, CCL2, CXCL10, PTGS2) and reduced oxidative stress, supporting mechanistic plausibility.[4] Human trial data on pain are mixed. A small open-label add-on study (30 mg/day with combined oral contraceptives) reported large pain improvements, but without a control group.[35] By contrast, a randomized, double-blind add-on trial (40 mg/day with combined oral contraceptives for 42 days) did not show additional pain relief versus placebo ($p = 0.7$).[30]

Antioxidant therapy with vitamins C and E has shown effectiveness in reducing oxidative stress and alleviating endometriosis-related pain. A RCT demonstrated that daily supplementation with 1000 mg of vitamin C and 400 IU of vitamin E over 8 weeks significantly reduced pelvic pain intensity. These findings were reinforced by a meta-analysis which confirmed consistent pain improvement across multiple RCTs.[7,18]

Vitamin D supplementation has demonstrated promise in alleviating endometriosis-related symptoms and modulating immune responses. A systematic review reported that doses ranging from 2000 to 4000 IU/day were associated with reductions in pelvic pain and inflammatory markers in several studies. Proposed mechanisms include modulation of T-cell subsets and suppression of aromatase activity, contributing to both immune balance and hormonal regulation.[19]

Melatonin, a neurohormone with antioxidant and anti-inflammatory properties, shows emerging promise as an adjunct in endometriosis care. A clinical trial using 10 mg/day of melatonin for 8 weeks demonstrated significant reductions in pelvic

TABLE 2 Botanical and Nutraceutical Interventions in Endometriosis

Study (Author, Year)	Intervention	Population	Study Type	Key Clinical Outcomes
Kamal et al., 2021*	Curcumin (500–1000 mg/day)	Female reproductive disorders	Narrative review	↓ TNF-α/NF-κB oxidative stress
Nodler et al., 2020*	Omega-3 (1000 mg/day)	Adolescents & young women with endometriosis	RCT (double-blind)	↓ pelvic pain (non-significant), ↑ quality of life
Sienko et al., 2024*	Resveratrol (40 mg/day) + COC for 42 days	Women with endometriosis	Systematic review	No reduction in pain vs placebo
Gołąbek-Grenda et al., 2024*	Resveratrol analogs in macrophage–endometriotic cell co-culture	Human cell co-culture	Preclinical (in vitro)	↓ pro-inflammatory cytokines, ↓ oxidative stress
Amini et al., 2021*	Vitamin C (1000 mg/day) + Vitamin E (400 IU/day)	Women with endometriosis	RCT (triple-blind)	↓ pelvic pain, ↓ oxidative stress markers
Zheng et al., 2023*	Vitamin C + E	Women with endometriosis	Systematic review & meta-analysis	↓ pelvic pain across studies
Kalaitzopoulos et al., 2022*	Vitamin D (2000–4000 IU/day)	Women with endometriosis	Systematic review	Mixed clinical effects; ↓ inflammatory markers in some studies
Li et al., 2022*	Melatonin (10 mg/day)	Women with endometriosis	Narrative/mechanistic review	↓ pelvic pain, ↓ analgesic use (from RCTs)
Liu et al., 2023*	Short-chain fatty acids (SCFAs)	Animal models	Preclinical	↓ lesion size, ↓ inflammation, ↑ gut barrier integrity
Norfuad et al., 2023*	Probiotic (*L. gasseri* OLL2809 10^9 CFU/day, 12 weeks)	Women with endometriosis	Review	↓ pelvic pain, ↓ lesion volume (reported)
Qing et al., 2022*	Microbiota-targeted strategies	Women with endometriosis	Systematic review	Support for adjunctive microbiome-based therapies
Iavarone et al., 2023*	Microbiota-targeted strategies	Women with endometriosis	Narrative review	Support for microbiota modulation in endometriosis

Studies marked with an asterisk (*) were directly discussed in the manuscript text.
IU: international units; SCFAs: short-chain fatty acids; RCTs: randomized controlled trials; TNF-α: tumor necrosis factor alpha; NF-κB: nuclear factor kappa B; COC: combined oral contraceptives

pain and analgesic use. Mechanistically, melatonin may act by suppressing inflammatory cytokines (e.g., IL-6, TNF-α), reducing COX-2 and aromatase activity, enhancing antioxidant defenses, and modulating reproductive tissue signaling through MT1 and MT2 receptors.[20]

Emerging research highlights a bidirectional relationship between gut microbiota and endometriosis pathophysiology, with dysbiosis contributing to inflammation, altered estrogen metabolism, and immune dysfunction. Preclinical findings suggest that short-chain fatty acids (SCFAs), particularly butyrate, may reduce lesion development and inflammation by strengthening gut barrier integrity and modulating macrophage activity. Although clinical trials on SCFAs are lacking, probiotic interventions show early promise. A trial found that *Lactobacillus gasseri* OLL2809 (10^9 CFU/day for 12 weeks) reduced pelvic pain and lesion volume. Other reviews suggest support for microbiota-targeted strategies as safe adjuncts in endometriosis care.[21-24]

Proposed Mechanisms

- Suppression of inflammatory cytokines (e.g., IL-6, TNF-α) via NF-κB and COX-2 inhibition[4,10,42]
- Antioxidant effects through scavenging of reactive oxygen species and upregulation of endogenous defenses[4,17,31]
- Modulation of estrogen synthesis and metabolism (e.g., aromatase inhibition)[3,33]
- Immunomodulatory activity, including T-cell regulation and macrophage polarization[4,21,23,33]
- Support of reproductive tissue integrity and neuromodulation via hormone receptor signaling (e.g., melatonin receptors)[6,43]
- Anti-inflammatory lipid mediators and prostaglandin modulation[16,30]
- Microbiota/SCFA-mediated barrier and immune modulation[21,41]

Acupuncture and Traditional Chinese Medicine Approaches

Acupuncture and TCM herbal therapies are increasingly used as non-pharmacologic approaches to manage endometriosis-related pain. A network meta-analysis, which included 25 RCTs, found that acupuncture-related therapies—such as manual acupuncture, electroacupuncture, and moxibustion—significantly reduced pelvic pain and dysmenorrhea compared with placebo or conventional medications (Table 3). Reported protocols commonly involved needle retention for 20–30 minutes, 2–3 sessions per week, over 4–12 weeks, with points such as CV4, SP6, ST36, and EX-CA1 frequently used.[13]

Similarly, a systematic review of TCM formulas including *Dan'e-fukang* soft capsules and *Gui Zhi Fu Ling Wan* reported consistent improvements in pelvic pain, estradiol regulation, and endometrial receptivity.[8] Both acupuncture and herbal TCM therapies were associated with favourable safety profiles and may offer individualized, adjunctive support in endometriosis care.

Proposed Mechanisms

- Neuromodulation of central pain pathways via acupuncture-induced effects on the hypothalamic–pituitary–adrenal (HPA) axis[44,49]
- Downregulation of pro-inflammatory mediators (e.g., IL-1β, IL-6, TNF-α)[8]
- Inhibition of COX-2 and NF-κB signaling (via herbal compounds)[10,30,47,48]
- Regulation of estrogen and prostaglandin synthesis[8]
- Enhancement of pelvic blood flow and uterine perfusion[45,46]

Lifestyle and Mind–Body Interventions

Lifestyle modifications and mind–body therapies represent a growing area of interest in endometriosis care, particularly for their ability to reduce stress-related inflammation and improve quality of life without pharmacologic side effects.

Yoga, mindfulness-based interventions (MBIs), and cognitive behavioural therapy (CBT) have shown beneficial effects on pain and psychological distress (Table 4). A narrative review summarized data from randomized trials and pilot studies, reporting that structured yoga practice—typically 90-minute sessions twice weekly for 8 weeks—led to significant reductions in pain intensity and improvements in quality of life. A narrative synthesis further emphasized the role of MBIs and CBT in addressing anxiety, depression, and pain catastrophizing, potentially through mechanisms such as cortisol regulation, vagal tone enhancement, and central pain modulation.[25,26]

A systematic review found that multi-modal self-management strategies—including education, physical activity, sleep hygiene, and behavioural techniques—were associated with tangible improvements. One trial reported a decrease in pain from 7.2 to 4.9 on a 10-point scale following an 8-week program, alongside gains in coping confidence and mental health.[27] Although the

TABLE 3 Acupuncture and Traditional Chinese Medicine Interventions in Endometriosis

Study (Author, Year)	Intervention	Population	Study Type	Key Clinical Outcomes
Su et al., 2025*	Manual acupuncture, electroacupuncture, moxibustion (20–30 min; 2–3×/week; 4–12 weeks; points: CV4, SP6, ST36, EX-CA1)	Women with symptomatic endometriosis	Systematic review & network meta-analysis (23 RCTs)	↓ pelvic pain, ↓ dysmenorrhea, improved QOL
Momenimovahed et al., 2024*	*Dan'e-fukang, Gui Zhi Fu Ling Wan* (formulae vary)	Women with endometriosis	Systematic review	↓ pelvic pain, estradiol regulation, ↑ endometrial receptivity
Desai et al., 2024	Holistic TCM & self-care strategies	Women with endometriosis	Narrative review	Potential benefits on pain and QOL (limited empirical detail)

Studies marked with an asterisk (*) are directly cited in the manuscript.
RCTs: randomized controlled trials; TCM: Traditional Chinese Medicine; QOL: quality of life

overall evidence base remains limited by small sample sizes and heterogeneous designs, these interventions are generally low-risk, align with naturopathic principles, and may complement conventional therapies in a comprehensive, patient-centred care model.

Proposed Mechanisms

- Modulation of central pain processing and neuroplasticity[50]
- Reduction of cortisol and sympathetic nervous system activity[51]
- Enhancement of vagal tone and parasympathetic regulation[52,53]
- Improvement in sleep quality and stress resilience[20,43]
- Support for behavioural self-regulation and emotional coping[54]

DISCUSSION

Summary of Key Findings

This narrative review synthesized findings from 27 clinical studies, including RCTs, systematic reviews, and narrative analyses, evaluating integrative approaches for endometriosis. Anti-inflammatory dietary strategies, such as the Mediterranean and low-FODMAP diets, demonstrated reductions in pain intensity and systemic inflammation.[2,12] Nutraceutical interventions—including omega-3 fatty acids, curcumin, resveratrol, and antioxidant vitamins (C, D, and E)—were associated with improvements in pelvic pain, oxidative stress markers, and hormonal balance, with generally favourable safety profiles.[10,16,17,19] Acupuncture and TCM showed efficacy in pain relief, menstrual regularity, and hormonal modulation, with strong safety profiles and potential for individualized care.[8,13] Lifestyle and mind–body therapies, including yoga, mindfulness-based stress reduction, and multi-modal self-management programs, improved patient-reported outcomes such as quality of life, anxiety, and pain coping confidence.[25,27]

Overall, these interventions collectively target core pathophysiological mechanisms in endometriosis—including inflammation, oxidative stress, hormonal imbalance, and immune dysregulation—and may offer safe, adjunctive options within naturopathic care frameworks.

Limitations in the Evidence Base

Although findings to date are encouraging, the current evidence base is constrained by several methodological limitations. Many studies were underpowered due to small sample sizes, lacked uniform outcome measures, and varied considerably in intervention type, dosage, and duration. Most trials were short-term, limiting conclusions about long-term efficacy, recurrence prevention, and sustainability. Furthermore, few studies directly compared integrative therapies with standard medical treatments, and data on multi-modal or combined naturopathic protocols remain scarce. These limitations hinder generalizability and the ability to translate findings into routine clinical practice.

Implications for Naturopathic Clinical Practice

Naturopathic doctors are uniquely positioned to provide individualized, integrative care for patients with endometriosis. The interventions reviewed—ranging from anti-inflammatory nutrition and targeted supplementation to acupuncture and mind–body therapies—demonstrate favourable safety profiles and multi-mechanistic actions. These features make them well-suited as adjuncts to conventional treatments. Clinical effectiveness may be enhanced by tailoring strategies to each patient's symptom burden, comorbidities, and therapeutic goals. Importantly, this integrative approach aligns with core naturopathic principles, including treating the whole person, supporting self-regulation, and addressing underlying drivers of chronic disease.

Recommendations for Future Research

To advance the clinical utility of integrative approaches for endometriosis, high-quality research is urgently needed.

Priority areas include:

- Differentiate by phenotype (primary addition): Stratify enrollment, outcomes, and analyses by deep infiltrating endometriosis (DIE)/endometriomas vs superficial lesions.
- Mechanism-matched endpoints: For invasive disease, include organ-specific symptoms and imaging/lesion metrics; for superficial disease, assess pelvic-floor function/tone, central sensitization, autonomic markers, and gastrointestinal (GI) comorbidity outcomes.
- Large, multi-center RCTs: To enhance statistical power, diversity, and external validity.
- Standardized protocols: Especially for botanicals, nutraceuticals, and mind–body therapies, to improve reproducibility and enable direct comparisons across studies.
- Longitudinal outcome studies: To evaluate durability of symptom relief, recurrence prevention, and long-term safety.

TABLE 4 Lifestyle and Mind–Body Interventions in Endometriosis

Study (Author, Year)	Intervention	Population	Study Type	Key Clinical Outcomes
Mazur-Bialy et al., 2024*	Yoga; 90-min sessions, 2×/week, 8 weeks	Women with endometriosis	Systematic search & narrative review	↓ Pain intensity, ↑ quality of life, improved stress markers
Mardon et al., 2023*	Multimodal self-management (education, PA, sleep hygiene, CBT); 8-week programs	Women with endometriosis	Systematic review	↓ Pain (7.2→4.9), ↑ mental health, ↑ coping confidence
Desai et al., 2024*	MBIs, CBT (no fixed protocol)	Women with endometriosis	Narrative perspective	↓ Anxiety, ↓ depression, ↓ catastrophizing, ↑ emotional regulation

Studies marked with an asterisk (*) were directly cited in the manuscript.
PA: physical activity; CBT: cognitive behavioral therapy; MBIs: mindfulness-based interventions; RCTs: randomized controlled trials

- Mechanistic investigations: Clarifying how integrative interventions influence inflammatory, hormonal, immune, and neuroendocrine pathways.
- Pragmatic and real-world trials: Assessing effectiveness of multimodal naturopathic strategies in everyday clinical practice.

Such efforts will strengthen the evidence base, facilitate clinical translation, and support the thoughtful integration of naturopathic therapies into mainstream gynecological care.

CONCLUSION

Endometriosis remains a complex, multifactorial condition with far-reaching implications for reproductive, physical, and psychosocial health. Although conventional therapies offer symptomatic relief, persistent pain, recurrence, and diminished quality of life remain common. Integrative approaches may provide more comprehensive, sustainable management options when grounded in robust clinical evidence.

This narrative review highlights growing clinical evidence supporting naturopathic and integrative interventions—encompassing dietary modification, botanical and nutraceutical supplementation, acupuncture, and lifestyle therapies—as adjunctive strategies in the management of endometriosis. Interventions such as the Mediterranean and low-FODMAP diets, omega-3 fatty acids, curcumin, resveratrol, vitamins C, D, and E, acupuncture, and yoga have demonstrated benefits across multiple clinical outcomes, including pain reduction, inflammation control, hormonal regulation, and psychosocial well-being.

These therapies appear to exert their effects through overlapping mechanisms, including modulation of immune function, reduction of oxidative stress, and support for endocrine balance. While the current evidence base is limited by small sample sizes, variable methodologies, and short follow-up periods, the favourable safety profiles and high patient acceptability of these interventions underscore their relevance in clinical care.

For naturopathic and integrative practitioners, these findings reinforce the value of individualized, multimodal care tailored to the complex and multifactorial nature of endometriosis. As research continues to evolve, future rigorously designed studies with standardized outcomes are essential to establish best practices. In the meantime, the thoughtful incorporation of evidence-informed interventions may help address unmet needs and improve quality of life for individuals living with endometriosis.

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Considerations of Gut Microbiome and Cancer—Part 1: Exploring Its Role in Tumorigenesis and Treatment Responses

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ABSTRACT

The gut microbiota is a pivotal determinant of human health, influencing both local and systemic physiological processes. Understanding its composition and function is crucial for exploring its impact on diseases, including cancer. Dysbiosis—or imbalances in the gut microbiota linked to negative health outcomes—is increasingly implicated in the pathogenesis of various cancers through mechanisms such as chronic inflammation, immune modulation, and metabolic interactions. The gut microbiome plays a fundamental role in maintaining host health by influencing gut integrity, metabolism, and immune function, with accumulating evidence suggesting a direct impact on cancer development and also cancer drug metabolism, modulating both treatment efficacy and toxicity. This manuscript explores the interactions between the gut microbiome and cancer, focusing on its role in tumorigenesis and its influence on the efficacy of cancer treatments. We review the underlying mechanisms by which specific bacterial species promote tumour development and discuss the microbiome's role in modulating chemotherapy, immunotherapy and radiotherapy outcomes. The complex interplay between the gut microbiome and cancer therapy continues to reveal new avenues for improving treatment outcomes, and as microbiome science becomes increasingly integrated into oncology, future research should focus on identifying specific microbial signatures predictive of treatment response, developing targeted microbiome-modulating interventions, and incorporating microbiome profiling into clinical trial design.

Key Words Gut microbiota, dysbiosis, microbial metabolites, host-microbiome-drug interactions

INTRODUCTION

Overview of the Human Gut Microbiota and its Microbiome

The term "microbiota" refers to the overall microbial taxa associated with humans[1] and therefore, "gut microbiota" refers to the large range of microorganisms inhabiting the gastrointestinal tract (GIT).[2] Each host shares a unique, generally symbiotic relationship with its microbiota.[3] These microbial communities, which can act as health-promoting microorganisms, innocuous commensals, or opportunistic pathogens,[2] reside within the various epithelial surfaces of the human body (skin, airways, urogenital tract, oral and nasal cavities). It is well established that the majority of human microbiota reside in the GIT, particularly in the large intestine,[4,5] and that both microbial density and diversity within the GIT increase from the proximal to the distal gut.[6] Figure 1 illustrates the microbial density and diversity throughout the human GIT.

Composition of the Gut Microbiota

The human gut microbiota is a complex and diverse community consisting of an estimated 10^{13} to 10^{14} microorganisms.[7,8] Bacteria are the predominant microbes, which also include viruses, fungi, protozoa, and archaea. This dynamic ecosystem is home to more than 1000 distinct bacterial phylotypes dominated by up to 10 bacterial phyla.[9,10] It has been reported that 90% of the total gut microbial population is often constituted by two phyla, Bacteroidetes and Firmicutes.[7,11] The other major phyla are often Actinobacteria, Proteobacteria and Verrucomicrobia.[7,11,12] Facultative anaerobic and anaerobic microorganisms populate the healthy adult gut. Gram-negative rods (belonging to genera *Bacteroides, Fusobacterium* and *Enterococcus*) and anaerobic Gram-positive bacteria (including *Lactobacilli* and *Streptococci*) are present in abundance, while *Bifidobacterium* species may account for up to 25%[13,14] (see Table 1).

The gut microbiota undergoes continuous adaptive remodelling, supporting a bidirectional, mutually beneficial symbiosis with the

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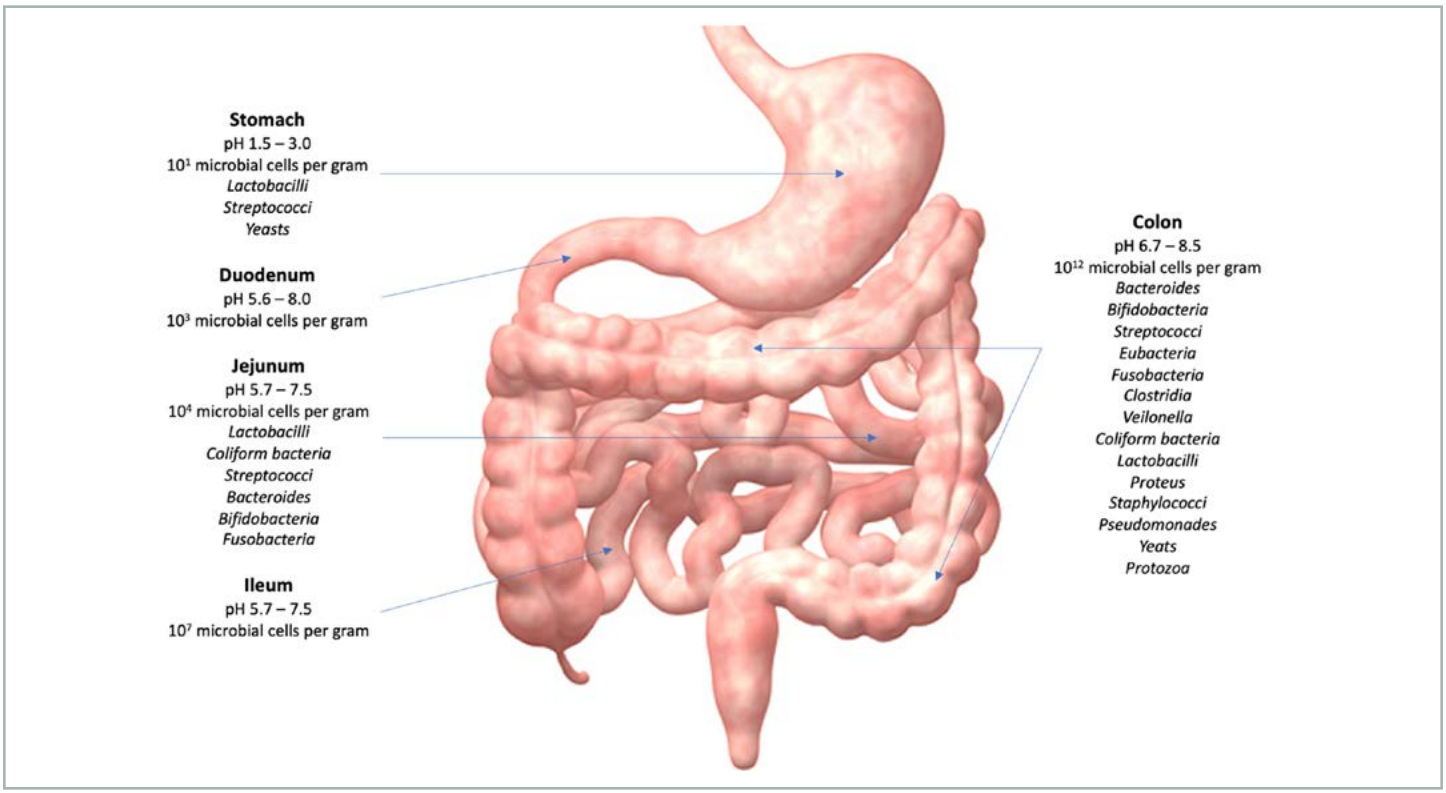

FIGURE 1 Microbial Density and Diversity at Various Sites Within the Gastrointestinal Tract

TABLE 1 Major Bacterial Phyla of the Human Gut Microbiota and Their General Actions

Major phyla	Representative examples	Actions
Bacteroidetes	*Bacteroides* and *Prevotella*	Regulation of immune responses and carbohydrate metabolic pathways.
Firmicutes	*Lactobacillus* and *Faecalibacterium*	Production of short-chain fatty acids and maintenance of epithelial barrier function.
Actinobacteria	*Bifidobacterium*	Facilitation of nutrient digestion and biosynthesis of bioactive metabolites.
Proteobacteria	*Escherichia* and *Helicobacter*	Potential pathobiont activity under dysbiotic or immunocompromised states.
Verrucomicrobia	*Akkermansia*	Support of epithelial homeostasis and host metabolic regulation.

host. There is significant variation in microbial diversity within populations,[15,16] and composition is influenced by factors such as genetics, age, medication use, nutritional status, and physical activity.[17] A balanced gut microbiota supports various physiological processes, including regulating metabolism and maintaining intestinal homeostasis. The GIT also acts as a major immune organ, containing up to 80% of the body's immune cells and helping to maintain systemic immune balance despite constant exposure to exogenous antigens.[1]

However, altered microbial balance can disturb communications between host and microbiota. The term "dysbiosis" refers to a perturbation [of the microbiota], marking a detrimental shift in its composition and/or function. Some researchers use the term "pathobiosis" to describe this disturbed microbial state. Petersen and Round define dysbiosis as "any change to the composition of resident commensal communities relative to the community found in healthy individuals."[19] However, such definitions tend to be broad and non-specific, which can create ambiguity about the role of dysbiosis in disease or may lead to inappropriate correlations between illness and microbial profiles. At present, our understanding of the mechanisms underlying these associations remains limited, making it difficult to determine whether dysbiosis is a cause or consequence of disease.[20]

Dysbiosis has been linked to inflammatory bowel disease, irritable bowel syndrome, and colorectal cancer (CRC).[21,22] Growing evidence illustrates that the influence of GIT microbiota extends beyond the gastrointestinal system, affecting neurological, musculoskeletal and cardiovascular disorders. Microbiome imbalances have been implicated in obesity, diabetes, Alzheimer's and Parkinson's diseases, depression, rheumatoid arthritis and sarcopenia.[23-26] An overgrowth of pathogenic populations can disrupt various metabolic and nutrient signalling pathways and promote chronic inflammation and DNA damage, processes that have been linked to carcinogenesis.[27]

Functions of the Gut Microbiome

Often incorrectly used interchangeably with "microbiota," the term "microbiome" refers to the collective genomes of the microorganisms residing in a specific habitat[28] and the metabolic capabilities they provide.[29] Collectively, the genes in the microbiome outnumber those in the human genome by at least 150-fold. The

gut microbiome alone is estimated to contain 3.3 million non-redundant genes[11] compared with the approximately 22,000 in the human genome.[30] This vast genetic reservoir supports a wide array of metabolic and biochemical functions, significantly contributing to host physiology, with a metabolic capacity comparable to that of the liver.[15]

The gut microbiome performs a range of essential functions that impact overall health and disease susceptibility. It is involved in immune system conditioning, drug metabolism and protection against epithelial cell injury.[31,32]

Metabolic Functions

Gut bacteria assist in the digestion of complex carbohydrates, producing short-chain fatty acids (SCFAs) such as butyrate, acetate, and propionate from fermentation of dietary fibres, which provide energy to colonocytes and exert anti-inflammatory effects. Microbial metabolism influences the biosynthesis and absorption of essential nutrients, including vitamin K and B vitamins (e.g., pyridoxine, cobalamin, folate, biotin). Gut microbial enzymes modify bile acids, impacting lipid digestion, cholesterol homeostasis and systemic metabolic pathways.

Immune System Modulation

The microbiome plays a critical role in the establishment and maintenance of immune tolerance, modulating the equilibrium between pro-inflammatory and anti-inflammatory responses. Intestinal microbiota are instrumental in educating the immune system to discriminate between pathogenic organisms and commensal microbes. Gut microbes influence adaptive immune responses, promoting the differentiation of CD4+ and CD8+ T cells.[33] Commensal bacteria, including *Lactobacillus*, support immune homeostasis by inducing and activating regulatory T cells, while *Clostridium* species increase production of interleukin (IL)-17 through proliferation of intestinal T helper (TH)17 cells.[34] Specific bacterial taxa, including *Bacteroides fragilis* and *Faecalibacterium prausnitzii*, produce immunomodulatory metabolites, such as SCFAs, indoles, and polysaccharides, that modulate immune signalling cascades and attenuate inflammatory processes, while *Bifidobacterium* species stimulate B cells to release secretory immunoglobulin A (IgA).[35]

Epithelial Barrier Integrity

The gut microbiome reinforces intestinal barrier function by promoting mucus secretion and enhancing the integrity of tight junctions between epithelial cells. Specific commensal bacteria, such as *Akkermansia muciniphila*, stimulate goblet cell activity and mucus layer production, thereby fortifying the mucosal barrier.[36] Additionally, beneficial microbes confer protection against pathogenic invasion by excluding harmful organisms through nutrient competition and occupation of epithelial binding sites.[37] Microbiota-derived metabolites—including SCFAs and antimicrobial peptides such as P-glycoprotein (P-gp)—further enhance epithelial cohesion and barrier integrity. SCFAs modulate the expression and function of tight junction proteins, including claudins and zonula occludens, which enhance barrier function, while P-gp modulates the movement of xenobiotics and bacterial toxins across the intestinal mucosa.[38,39] Compromised intestinal barrier integrity can facilitate the translocation of microbial components and metabolites, such as lipopolysaccharide (LPS) and trimethylamine (TMA), into the systemic circulation. LPS, a glycolipid endotoxin derived from the outer membrane of many gram-negative pathogenic bacteria, exerts potent proinflammatory effects and further disrupts epithelial barrier function.[40] TMA, a metabolite generated by gut microbiota from dietary choline, is subsequently oxidized in the liver to form trimethylamine-N-oxide (TMAO), a compound strongly implicated in the pathogenesis of cardiometabolic disorders and CRC.[6,41]

RATIONALE FOR INVESTIGATING THE GUT MICROBIOME'S INFLUENCE ON CANCER TREATMENT

The microbiome is increasingly recognized as a key modulator in the pathophysiology of numerous human diseases, including cancer. Emerging evidence highlights its significant influence on the efficacy of cancer therapies, with studies indicating that modulation of the gut microbiome can alter therapeutic responses across various treatment modalities.[42] Microbial-derived metabolites have been shown to influence tumour microenvironments, affecting gene expression, cell cycle regulation and apoptosis.[43] By altering drug metabolism, the gut microbiome can modulate the bioavailability and efficacy of chemotherapeutic and immunotherapeutic agents, leading to enhanced immune responses and mitigation of treatment toxicities.[44] A better understanding of an individual's microbiome could lead to more tailored and effective cancer treatments, which are increasingly explored in the emerging fields of personalized medicine and pharmacomicrobiomics.[45,46]

Several recent papers have described relationships between altered gut microbial composition and various malignancies, including gastrointestinal and hematological cancers.[47,48] Accumulating evidence indicates that the gut microbiome can modulate host immune responses, influencing outcomes across a spectrum of oncologic treatments, including chemotherapy, immunotherapy, and radiotherapy,[49] and the gut microbiome has been proposed as a potential biomarker in cancer therapy.[50,51] This narrative review summarizes current literature examining the relationship between the gut microbiome and its role in cancer development and therapeutic response. Relevant studies were identified through non-systematic searches of PubMed, Scopus, and Google Scholar using keywords such as "gut microbiome," "cancer," "gut microbial metabolites," and "host-microbiome drug interactions." Priority was given to peer-reviewed review articles and original research published in the past 5 to 10 years, although earlier foundational studies were included where appropriate. Articles were selected based on relevance and contribution to key themes, without formal inclusion or exclusion criteria or a systematic protocol. This manuscript aims to examine how the human gut microbiome contributes to cancer pathogenesis and explores how various microbial-derived metabolites interact with cancer treatments, influencing drug metabolism, therapeutic response, and resistance.

DYSBIOSIS AND ITS ROLE IN CANCER DEVELOPMENT AND PROGRESSION

Dysbiosis has been increasingly recognized as a contributing factor in cancer development and progression, either through direct cellular interactions or the secretion of bioactive metabolites.[43] This disruption in gut microbial homeostasis can result in an inflammatory environment, immune dysfunction and metabolic alterations, which may contribute to tumorigenesis. A reduction in beneficial bacteria (*Lactobacillus, Bifidobacterium*) and increased levels of pathogenic bacteria (*Fusobacterium nucleatum, Escherichia coli*) have been associated with immune evasion and tumour growth.[52] Dysbiosis can promote chronic, systemic, low-grade inflammation by increasing the production of pro-inflammatory cytokines IL-6, IL-1β, and tumour necrosis factor (TNF)-α.[35] *Helicobacter pylori* infection is a well-documented cause of gastric cancer, promoting tumorigenesis through chronic inflammation and activation of oncogenic pathways like β-catenin signalling.[53] An overabundance of *Enterococcus faecalis, E. coli, B. fragilis* and *Campylobacter* has been implicated in developing CRC.[54,55] These bacteria drive tumorigenesis by inducing inflammation[56] and through the production of genotoxins—toxic compounds that cause DNA damage and disrupt DNA repair mechanisms—including colibactin and cytolethal distending toxin (CDT).[52] Further, *F. nucleatum* enhances colorectal carcinogenesis progression through the actions of FadA and Fap2, adhesins that promote proliferation and immune evasion.[57]

MICROBIAL METABOLITES AND THEIR IMPACT ON TUMORIGENESIS

Bioactive metabolites, generated from dietary components and microbial metabolic pathways, can influence cancer development and progression by affecting inflammation, immune response, and cellular signalling. Several important classes of microbial metabolites have been identified as key players in tumorigenesis, acting either as tumour-promoting or tumour-suppressing agents.

Short-Chain Fatty Acids

SCFAs are produced by microbial fermentation of non-digestible dietary fibre by gut bacteria and exert significant effects on cancer biology. The most abundant SCFAs, butyrate, acetate and propionate, constitute approximately 90% of the SCFAs produced by the microbiome.[58] Butyrate, produced by bacteria such as *F. prausnitzii, Roseburia intestinalis,* and *Agathobacter rectale*, serves as a primary energy source for colonic epithelial cells.[59] Butyrate supports mucosal integrity, preventing microbial translocation and systemic inflammation.[60] At low concentrations, butyrate has been shown to inhibit histone deacetylases (HDACs), leading to increased apoptosis and reduced proliferation of cancer cells, particularly in CRC.[61,62] Animal models have demonstrated that SCFAs enhance regulatory T-cell (Treg) differentiation and promote an anti-inflammatory microenvironment, which can attenuate tumour progression.[63] In clinical trials, patients with advanced colorectal adenoma were found to have reductions of the main butyrate-generating taxa (*Clostridia, Firmicutes, Eubacterium*) and reduced fecal butyrate.[64] A 2015 systematic review by Borges-Canha et al. reported that decreased butyrate and a microbial profile with reduced representation of butyrate producers were associated with colorectal carcinogenesis.[65] Table 2 provides a summary of the mechanisms of gut microbiota-derived metabolites.

Bile Acid Metabolites

The gut microbiome modifies primary bile acids into secondary bile acids, which can have pro-carcinogenic effects.[92] Colonic bacteria within the phylum Firmicutes have demonstrated 7-dehydroxylation activity, capable of metabolizing cholic and chenodeoxycholic acids into deoxycholic acid (DCA) and lithocholic acid (LCA).[93] DCA and LCA have been linked to oxidative stress and DNA damage in colon epithelial cells, contributing to colorectal carcinogenesis.[94] These metabolites activate nuclear receptors like the farnesoid X receptor (FXR) and pregnane X receptor (PXR), influencing bile acid homeostasis and inflammation pathways associated with cancer.[95] Elevated DCA levels have been associated with the progression of CRC.[94]

Polyamines

Polyamines, such as putrescine, spermidine, and spermine, are synthesized through the decarboxylation of the amino acids, ornithine, arginine, and lysine. Depending on their circulating levels, polyamines can either promote normal cellular differentiation and intestinal mucosal integrity or contribute to tumorigenesis.[96] Elevated polyamine levels, which are linked with dysbiosis, have been associated with increased proliferation of cancer cells, reduced apoptosis and disruption of epithelial barrier integrity. Polyamines have induced oxidative stress, resulting in DNA damage and CRC in animal models.[97] Spermidine reduces the concentration of IL-18 in the colon and has been implicated in modulating chromatin structure and gene expression, affecting pathways involved in cancer progression.[96] Spermine has been associated with increased expression of catenin, involved in tumour cell proliferation.[98]

Indoles and Tryptophan Metabolites

Ingested tryptophan (TRP) that is not absorbed in the small intestine is metabolized by colonic bacteria into several bioactive indole derivatives, which have dual roles in tumorigenesis (tumour-suppressing and pro-carcinogenic effects). *Clostridium* and *Ruminococcus* have been shown to degrade TRP to tryptamine by the action of tryptophan dehydrogenase, and indole-3-acetic acid (IAA) is synthesized by species within *Bifidobacteria, Bacteroides* and *Eubacteria*.[99] Tryptophanase, expressed by certain *Bacteroides* and *Lactobacillus* species, generates indole-3-propionic acid (IPA), which has been shown to enhance gut epithelial integrity.[100] IAA, IPA, indole-3-aldehyde (I3A), indole-3-lactic acid (ILA) and indoxyl-3-sulfate serve as ligands for the activation of aryl hydrocarbon receptor (AhR), expressed on the surface of neutrophils, macrophages, dendritic cells and TH17 cells.[101] These metabolites mediate anti-inflammatory actions through

TABLE 2 Cancer-related mechanisms, actions and effects of gut microbiota-derived metabolites

Metabolite			Mechanism	Action	Effect	Reference
PAs	Spermine		Protect DNA, scavenge free radicals	↓ oxidative damage	Prevention of carcinogenesis	Ha et al, 1998[66]
PPDs	PAA		↑ cytotoxicity in tumour cells	↓ cell proliferation	Enhances apoptosis	Gao et al, 2019[67]
	4-hydroxyPAA		↑ cytotoxicity in tumour cells	↓ cell proliferation	↑ Anti-proliferative effect	Rupasinghe et al, 2019[68]
	DAT		↑ activated T cells and NK cells	↑ immune checkpoint inhibition	Delays tumour growth	Joachim et al, 2023[69]
SBAs			Inhibits NLRP3 inflammasome activation	↓ inflammation	Prevention of carcinogenesis	Guo et al, 2016[70]
	DCA		Activates c-Myc pathway	↑ β-catenin cell signalling pathway	Stimulates cancer cell proliferation	Cheng and Raufman, 2005[71]
	LCA		Activates TGR5 (Gpbar1), ↓ VEGF	↓ cell proliferation, impairs angiogenesis	Inhibits proliferation	Miko et al, 2018[72]
SCFAs			Activates cytotoxic CD8+ T cells	↓ anti-tumour immunity	T cell immunosuppression	Behary et al, 2021[73]
	Butyrate		Modulates CD8+ T cells	↑ anti-tumour immunity	Enhances adaptive immunotherapy	Luu et al, 2021[74]
	Butyrate		Modulates CD8+ T cells	↑ anti-tumour therapeutic effectiveness	Enhances anticancer effectiveness	He et al, 2021[75]
	Butyrate		Modulates CD8+ T cells	↑ anti-tumour therapeutic effectiveness	Enhances anticancer effectiveness	Kang et al, 2023[76]
	Butyrate		Modulates CD8+ T cells	↑ anti-tumour therapeutic effectiveness	Enhances anticancer effectiveness	Zhu et al, 2023[77]
	Butyrate		Inhibits T cell response	↓ anti-tumour immunity	↓ effectiveness of anticancer therapy	Coutzac et al, 2020[78]
	Formate		Activates AhR signaling	↓ anti-tumour immunity	Accelerates tumour expansion	Ternes et al, 2022[79]
	Butyric acid		↑ CTLs, ↓ Treg function	↑ anti-tumour immunity	Enhances anticancer effectiveness	Gao et al, 2023[80]
	Succinic acid		↓ cGAS-interferon-β pathway	↓ anti-tumour immunity	↓ tumour response to immunotherapy	Jiang et al, 2023[81]
TCs	TRP		Modulates CD8+ T cells	Activates AhR signaling	↓ anti-tumour immunity	Hezaveh et al, 2022[82]
	TRP		Modulates CD8+ T cells	↑ immune checkpoint inhibition	AhR agonist within TME	Bender et al, 2023[83]
	5-HT		↓ lipid peroxidation	↓ oxidative damage	Inhibits ferroptosis	Liu et al, 2023[84]
	IND derivatives	I3A	Modulates CD8+ T cells	↑ inflammation	↓ anti-tumour immunity	Mohseni et al, 2023[85]
		I3C	Activates AhR signaling	↑ anti-tumour therapeutic effectiveness	Enhances apoptosis	Megna et al, 2016[86]
		IAA	↑ ROS	↓ inflammation,	Enhances anticancer effectiveness	Tintelnot et al, 2023[87]
		ICA	Inhibits regulatory T cell activity	↑ anti-tumour immunity	Enhances anticancer effectiveness	Fong et al, 2023[88]
		ILA	Modulates CD8+ T cells	↓ inflammation, ↓ tumorigenesis	↑ anti-tumour immunity	Zhang et al, 2023[89]
		ILA	Activates apoptotic pathways	↓ cell proliferation	↓ tumorigenesis	Sugimura et al, 2022[90]
		ILA	↓ IL-17 pathway	↓ tumour burden	↓ tumorigenesis	Han et al, 2023[91]

↓ = suppress; ↑ = promote; 5-HT = serotonin (5-hydroxytryptamine); AhR = aryl hydrocarbon receptor; CTLs = cytotoxic T-lymphocytes; DAT = desaminotyrosine; DCA = deoxycholic acid; Gpbar = G-protein bile acid receptor; I3A = indole-3-aldehyde; I3C = indole-3-carbinol; IAA = indole-3-acetic acid; ICA = indole-3-carboxylic acid; IFN = interferon; ILA = indole-3-lactic acid; IND = indole; LCA = lithocholic acid; NK = natural killer; NLRP = NOD (nucleotide-binding oligomerization domain)-like receptor; PA = polyamine; PAA = phenylacetic acid; PPD = phenylpropanoid derivative; ROS = reactive oxygen species; SBA = secondary bile acid; SCFA = short-chain fatty acid; TC = tryptophan catabolite; TME = tumour microenvironment; TRP = tryptophan; VEGF = vascular endothelial growth factor.

AhR signalling, resulting in increased production of IL-22 and inhibition of LPS-induced IL-6 expression.[102,103] The tumour-suppressing actions of indole-3-carbinol (I3C) through accelerated apoptosis are well characterized.[104] Conversely, kynurenine, a tryptophan metabolite produced through the indoleamine 2,3-dioxygenase (IDO) pathway, has been linked to T-cell inhibition in the tumour microenvironment (TME), promoting cancer cell evasion from immune surveillance.[101] High expression of IDO and tryptophan 2,3-dioxygenase (TDO) in the TME can result in local tryptophan deficiency, immune suppression and tumour expansion and is associated with poor prognosis in patients with gastric adenoma.[105,106] Indeed, the use of IDO and TDO inhibitors to block tryptophan metabolism is currently being investigated in clinical trials.[107]

GUT MICROBIOME INFLUENCE ON CANCER TREATMENT

The gut microbiome shapes the metabolic fate of exogenous compounds. Gut microbes can modify therapeutic compounds directly as they pass through the GIT or influence their processing within the enterohepatic circulation,[108] influencing the pharmacokinetics of various cancer therapies. These modifications may lead to bioactivation or inactivation depending on the activity of enzymes expressed by resident microbes.[109] Further, the microbiome regulates host gene expression in both the liver and intestine, including those involved in detoxification pathways such as cytochrome P450 enzymes and multidrug resistance proteins.[110] The gut microbiome also affects drug absorption, distribution and elimination. It exerts these effects by modulating intestinal permeability, altering the expression of drug transporters and directly binding to the compounds.[111] Bacterial-derived metabolites, including SCFAs, bile acids, and polyamines, influence the expression of P-gp and other efflux transporters in the gut epithelium, affecting drug bioavailability.[112]

Inter-individual differences in drug response pose a significant challenge in cancer treatment. Accumulating evidence suggests that variability in gut microbiome characteristics influences drug response profiles.[113] Recent research on gut microbial co-metabolism indicates substantial within-species variation in bacterial capacity to metabolize drugs,[114] potentially explaining the wide variability in drug–microbiome interactions observed between individuals during treatment. Pharmacomicrobiomics is an emerging field that attempts to clarify the complex host–microbiome–drug interactions (HMDIs). It explores the molecular mechanisms that drive individual differences in clinical outcomes resulting from microbiota-mediated drug metabolism, while also examining how pharmaceutical agents, in turn, affect the composition and function of the microbiome.[45,115] It is well established that the microbiome exerts regulatory control over the biotransformation, bioavailability, absorption and distribution of a wide range of pharmaceuticals.[116,117]

Interactions of Gut Microbiome with Chemotherapy and Immunotherapy

Substantial pre-clinical and human evidence confirms the GIT microbial environment can influence the bioavailability, efficacy, and toxicity of cancer therapeutic agents. Enteric bacterial metabolism can either inactivate these drugs or alter their absorption, resulting in lower plasma concentrations and reduced therapeutic efficacy. Several well-characterized HMDIs provide insight into how the gut microbiome can influence cancer treatment outcomes.

Irinotecan (CPT-11) is a widely used prodrug chemotherapeutic for CRC. Hepatic carboxylation converts CPT-11 into its active form, SN-38, which is later inactivated by glucuronidation in the liver.[118] However, gut bacteria such as *E. coli* and *Clostridium* species express β-glucuronidases, which can deconjugate SN-38, leading to its reactivation in the intestine.[119] This process results in severe gastrointestinal toxicity, including diarrhea, which can limit treatment efficacy.[118] It is widely accepted that administration of cytotoxic agents results in changes to the gut microbiome.[120] However, chemotherapy can disrupt niche-specific competitive inhibition, permitting pathobionts to flourish, which in turn may contribute to drug-induced toxicity. For example, a 2017 study of tumour-bearing rats reported that increased abundances of pathobiont species *Fusobacteria* and *Proteobacteria* were detected following irinotecan administration.[121]

Gemcitabine (2',2'-difluorodeoxycytidine) is an antimetabolite used in the treatment of various solid tumours, including breast, lung, and ovarian cancers, which interferes with DNA replication, thereby halting the growth of rapidly dividing cancer cells.[122] *Gammaproteobacteria* were shown to metabolize gemcitabine into an inactive form (2',2'-difluorodeoxyuridine) through expression of cytidine deaminase, leading to treatment resistance.[122,123]

Methotrexate (MTX), an antimetabolite chemotherapy agent, is subject to microbial metabolism in the gut. MTX inhibits mammalian dihydrofolate reductase (DHFR) and has been shown to modify human GIT microbiota, which may elucidate differences in treatment responders and non-responders.[124] Genes expressed by *Firmicutes* and *Bacteroidetes* metabolize MTX, reducing its bioavailability, and may contribute to drug resistance.[125] Therefore, differences in GIT microbiome profiles may impact host therapeutic response outcomes.[126]

Cyclophosphamide (CTX), an alkylating agent used in various cancer therapies, is influenced by the immunomodulatory effects of gut microbiota. Gram-positive bacteria, including *Lactobacillus* and *Enterococcus* species, stimulate CTX-induced immune responses in the TME, indirectly promoting the activation of Th1 and Th17 cells and enhancing anti-tumour immunity.[127] *Barnesiella intestinihominis*, a gram-negative bacterium, stimulates the accumulation of tumour-specific cytotoxic CD8+ and CD4+ T cells and enhances the infiltration of interferon (IFN)–γ–producing T cells into the TME following CTX treatment.[128]

The gut microbiome shapes innate and adaptive immune responses, influencing immune homeostasis, regulating chronic inflammation and suppressing tumour growth. The interaction between the microbiota and the host immune system is complex, involving immune cell modulation, cytokine signalling pathways and various receptors, including pattern recognition receptors such as the Toll-like receptor (TLR) superfamily.

Bacterial taxa, including *A. muciniphila, B. fragilis, E. coli,* and *Lachnospiraceae* and *Bifidobacterium* species, exhibit anti-inflammatory properties and are associated with immune cell activation.[129] The gut microbiome modulates T-cell differentiation, influencing the balance between pro-inflammatory Th1/Th17 responses and anti-inflammatory Treg cells. *B. fragilis* produces polysaccharide A, which induces Treg differentiation and suppresses excessive inflammation. Segmented filamentous bacteria (SFB) promote Th17 responses, which can be beneficial for mucosal defense. Commensal bacteria, including *E. coli, Bifidobacteria* and SFB, stimulate B cell activation, leading to the production of IgA, which reinforces mucosal immunity by neutralizing pathogens and maintaining epithelial integrity.[130] Commensal bacteria interact with host immune cells through TLRs,

which helps maintain immune surveillance and inflammatory balance. *Bifidobacteria* and *Lactobacilli* promote the maturation of dendritic cells, enhancing antigen presentation and immune tolerance.[131] *Akkermansia* and *Bifidobacteria* stimulate dendritic cells, leading to improved antigen presentation and activation of cytotoxic T cells.[132]

Other microbes, including *F. nucleatum* and *Bacteroides vulgatus*, are associated with cancer progression, in part, by driving chronic inflammation and facilitating immune evasion.[57] While some *Bacteroides* species are beneficial, *B. fragilis* has been linked to immunotherapy resistance due to its role in suppressing immune responses and inducing regulatory T cells.[133] Further, *B. fragilis* augments phagocytosis, polarizing macrophages to an M1 state.[134] *Enterococcus faecalis* drives nuclear factor (NF)-κB pro-inflammatory pathways,[135] while *Peptostreptococcus anaerobius* has been shown to induce reactive oxygen species (ROS) formation and stimulate cell proliferation through activation of the PI3K-Akt pathway.[136,137]

Microbial metabolites such as SCFAs influence macrophage polarization, shifting them from a pro-inflammatory (M1) to an anti-inflammatory (M2) phenotype through histone acetylation, which promotes tissue repair and reduces inflammation.[138] SCFAs, particularly butyrate, produced by *F. prausnitzii* and *Ruminococcus,* reinforce Treg activity while simultaneously enhancing cytotoxic T lymphocyte infiltration into tumours.[139] Butyrate has been shown to inhibit the release of IL-6 and IL-12, modulate immune tolerance of colonic macrophages to commensal organisms,[62] and induce apoptosis in cancer cells, enhancing the efficacy of gemcitabine.[14]

The gut microbiome also significantly influences the response to immune checkpoint inhibitors (ICIs), which target lymphocyte-associated antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1) and its ligand (PD-L1). Perhaps unsurprisingly, an inverse correlation has been reported between antibiotic treatment and positive ICI outcomes in observational studies.[141-143] The abundance levels of specific bacterial species have been associated with enhanced efficacy of ICIs by promoting immune activation and improving therapy response rates.[144-146] Higher microbial diversity has been linked to improved responses to anti-PD-1 therapy in patients with lung and renal carcinoma; in particular, non-responders to PD-1 blockade were found to have low levels of *A. muciniphila.*[143] *A. muciniphila* enhances gut epithelial integrity, promotes immune system activation and inhibits inflammation.[147] Higher abundances of *Bifidobacteria* have been reported in patients responding to ICIs, which appear to promote dendritic cell activation and augment anti-tumour immune responses, although the specific mechanisms underlying these immunomodulating effects are still unknown.[148-150] Profiling of gut microbiota in melanoma patients receiving combined immune checkpoint blockade targeting PD-1 and CTLA-4 demonstrated a significantly higher abundance of *Bacteroides intestinalis* in patients with adverse events.[151]

Interactions of Gut Microbiome with Radiotherapy

Various factors, particularly immunological modulation, critically influence tumour progression and therapeutic response to ionizing radiation. Radiotherapy has been shown to induce immunogenic cell death, facilitating antigen release and enhancing the recruitment and infiltration of effector lymphocytes into the TME. Radiation therapy is a cornerstone of cancer treatment; however, its efficacy and side effects can be influenced by the gut microbiome. Radiation therapy, particularly for abdominal and pelvic cancers, can cause significant gastrointestinal side effects, including mucositis, diarrhea, and dysbiosis.[152] Radiation exposure often leads to dysbiosis, characterized by a relative decrease in the richness of favourable microorganisms, e.g., *Lactobacilli* and *Bifidobacteria*, and an increase in the richness of opportunistic pathogens, e.g., *Fusobacteria* and *Clostridium difficile*. Dysbiosis following radiation exposure may exacerbate radiation enteropathy, resulting from impaired epithelial integrity, bacterial translocation and systemic inflammation.[153] Mounting evidence suggests microbiome-mediated interactions impact both radiation sensitivity and toxicity, impacting treatment outcomes. Certain bacterial species can enhance tumour response to radiation therapy by modulating immune activity, oxidative stress and antioxidant responses, and augmenting DNA repair pathways.

A. muciniphila has been linked with improved responses to radiation due to its role in promoting anti-tumour immunity. Previous studies have demonstrated a positive correlation between relative abundances of *A. muciniphila* and clinical responses to radiotherapy.[128] SCFAs and other bacterial metabolites promote the expansion of regulatory Tregs, reducing the effectiveness of radiation-induced immune responses.[155] Chronic inflammation induced by pathogenic bacteria may activate NF-κB and signal transducer and activator of transcription (STAT)3 pathways, which promote tumour survival and resistance to radiation.[156]

Some bacterial metabolites can impact DNA repair pathways, making tumour cells more susceptible to radiation-induced damage. SCFAs, particularly acetate and butyrate, influence epigenetic modifications that upregulate DNA repair genes.[157] Conversely, certain bacteria can enhance the DNA repair capabilities of tumour cells, leading to increased radiation resistance.[158] *B fragilis,* for example, has been demonstrated to stimulate host cellular stress responses,[159] which may enhance the ability of cancer cells to repair radiation-induced DNA damage.

ROS generated during radiotherapy serve as key mediators of oxidative stress, inducing extensive molecular and cellular damage within tumour cells. The gut microbiome can modulate cellular antioxidant defenses, enhancing radiation-induced tumour cell death and reducing radiation sensitivity. The antioxidant capacity of several *Lactobacilli* strains has been described, which includes producing ROS-scavenging metabolites and regulating antioxidant enzyme activity and signalling pathways.[160,161] In murine models, *L. casei* increased superoxide dismutase (SOD) and glutathione peroxidase (GPx) activity, while *L. plantarum* could attenuate oxidative stress induced by D-galactose.[162,163] Early in-vitro studies demonstrated *L. acidophilus* is capable of protecting against lipid peroxidation, and *L. fermentum* species were shown to have SOD activity.[164,165] Further, some bacteria affect host iron regulation, impacting the Fenton reaction and decreasing the generation of cytotoxic free radicals.[16] Interestingly, most

pathogenic GIT bacteria possess enhanced systems for acquiring free iron, enabling them to outcompete commensal microbiota. Iron deficiency anemia is a common clinical manifestation of CRC patients, necessitating iron supplementation. However, the route of iron administration may contribute to a pro-carcinogenic microbial profile.[167] Oral supplementation can increase the amount of iron directly available to gut microbes, leading to the proliferation of oncogenic species.[168] This microbial shift is less likely following intravenous administration, which doesn't increase luminal iron.[169]

Future Directions for Integrating Microbiome Science into Oncology

The gut microbiome is central in regulating metabolic, immune, and inflammatory processes. Gaining deeper insight into host–microbiome–drug relationships may lead to innovative microbiome-targeted strategies that enhance oncologic treatment efficacy. Emerging evidence supports the utility of microbial signatures as predictive biomarkers for treatment response, representing a promising frontier in precision oncology. As the field advances, the integration of microbiome-informed diagnostics and therapeutics into clinical workflows may enable more effective, personalized treatment paradigms tailored to individual microbiota profiles. By leveraging microbiome insights, clinicians can refine therapeutic approaches, enhance patient outcomes, and minimize treatment-related complications, moving toward a more precise and individualized approach to oncology care.

CONCLUSION

The gut microbiome is a critical modulator of host physiology, exerting both local and systemic effects by preserving intestinal epithelial barrier integrity, regulating host metabolic homeostasis, and modulating innate and adaptive immune responses. Dysregulation of the gut microbiome is increasingly implicated in the initiation and progression of various malignancies, mediated through mechanisms including chronic inflammation, disruption of immune homeostasis, and alterations in microbial metabolic activity. The human microbiome may directly contribute to oncogenesis by modulating anti-tumour immune surveillance and shaping host responses to treatment. Microbial-mediated drug resistance is an ongoing concern in cancer therapy. The current review described several bidirectional interactions between the gut microbiome and cancer, highlighting the microbiota's capacity to influence the pharmacokinetics of anticancer therapies, thereby affecting treatment efficacy and toxicity profiles. Gut microbial enzymes may directly modify drugs as they pass through the intestinal tract before they reach their target or indirectly by affecting detoxification pathways within the enterohepatic circulation, impacting drug clearance mechanisms. A better understanding of HMDIs could lead to enhanced treatment outcomes by enabling the development of personalized microbiome-targeted therapies, such as identifying microbial biomarkers that predict drug efficacy or toxicity, engineering probiotics to modulate specific immune pathways, and tailoring antibiotic or dietary interventions to preserve beneficial microbial communities during treatment.

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The WHO's Expedition into Traditional Medicine—A Naturopathic Observation

Iva Lloyd,[1] ND

INTRODUCTION

The World Health Organization's (WHO) expedition into the vast field of traditional medicine (TM) began in the late 1970s. Since that time, there have been significant advances in the WHO's engagement and directives to member states (i.e., Ministries of Health) globally, especially in the last few years. As depicted in Figure 1, notable initiatives include the Primary Health Care Declarations; the WHO's First Traditional Medicine Global Summit, and the WHO Traditional Medicine Strategies.

PRIMARY HEALTH CARE DECLARATIONS

The two International Conferences on Primary Health Care (PHC) held in 1978[1] and 2018[2] resulted in the Alma-Ata Declaration[1] and the Astana Declaration,[2] respectively. These declarations serve as a forty-year roadmap for health care as they outline the collective focus of Ministries of Health, health experts and global organizations. The 1978 International Conference was a landmark event, as it was the first international declaration underlying a global commitment to health equity and PHC.[1]

At the 2nd International Conference, the progress reported since the Alma-Ata Declaration included:[3]

- Recognition that health is directly correlated with economic growth and development.
- An increase in life expectancy, a decrease in maternal and child mortality and a decrease in many infectious diseases.
- A dramatic rise in non-communicable diseases and mental health issues, which was attributed to a focus on treating specific diseases at the expense of prevention and addressing the determinants of health.

The areas of focus necessary to achieve global PHC and universal health care (UHC) included the following:[3]

- Prevention and non-communicable diseases
- Patient-centred health care and increased health literacy
- Determinants of health
- Self-responsibility and sustainability
- Need to address global burdens of disease, such as antimicrobial resistance

Unlike the Alma-Ata Declaration, the Astana Declaration included a call for increased collaboration and cooperation between the public and private healthcare systems and between different aspects of health care and a need to embrace technology, including e-health.[2] As President of the World Naturopathic Federation (WNF) at that time, I was fortunate to attend this conference along with Professor and Naturopathic Doctor Jon Wardle. It was apparent that the discussions, especially the recommendations for future steps, were very much in line with the naturopathic and TM approach to health care,[4] and yet discussion of TM was mostly absent from the conversation. Traditional medicine was referenced in the list of health workers in the Alma-Ata Declaration,[1] and traditional knowledge and traditional products were mentioned in the Astana Declaration,[2] but the focus on TM was minimal. Another notable omission in the 2018 Conference and in the Astana Declarations was environmental health.

First WHO Traditional Medicine Global Summit

Despite having a TM department at the WHO since the 1980s, the first WHO Traditional Medicine Global Summit (Summit) was held in August 2023 in Gandhinagar, India.[4] Just prior to the Summit, the WHO Global Traditional Medicine Centre was established in Jamnagar, Gujarat, India, as a knowledge centre for TM focusing on evidence and learning, data and analytics, sustainability and equity, and innovation and technology in order to optimize the role of TM in PHC globally.[5] The goal of the Summit was to mobilize political commitment and action to integrate TM into PHC and to improve UHC using evidence-based TM products and practices.[5] The Summit marked a significant change in the WHO's inclusion of TM in PHC and UHC.

WHO Traditional Medicine Strategies

The main WHO documents that impact TM professions are the WHO Traditional Medicine Strategies (Strategies). There have been three Strategies. The first one set TM strategic objectives for

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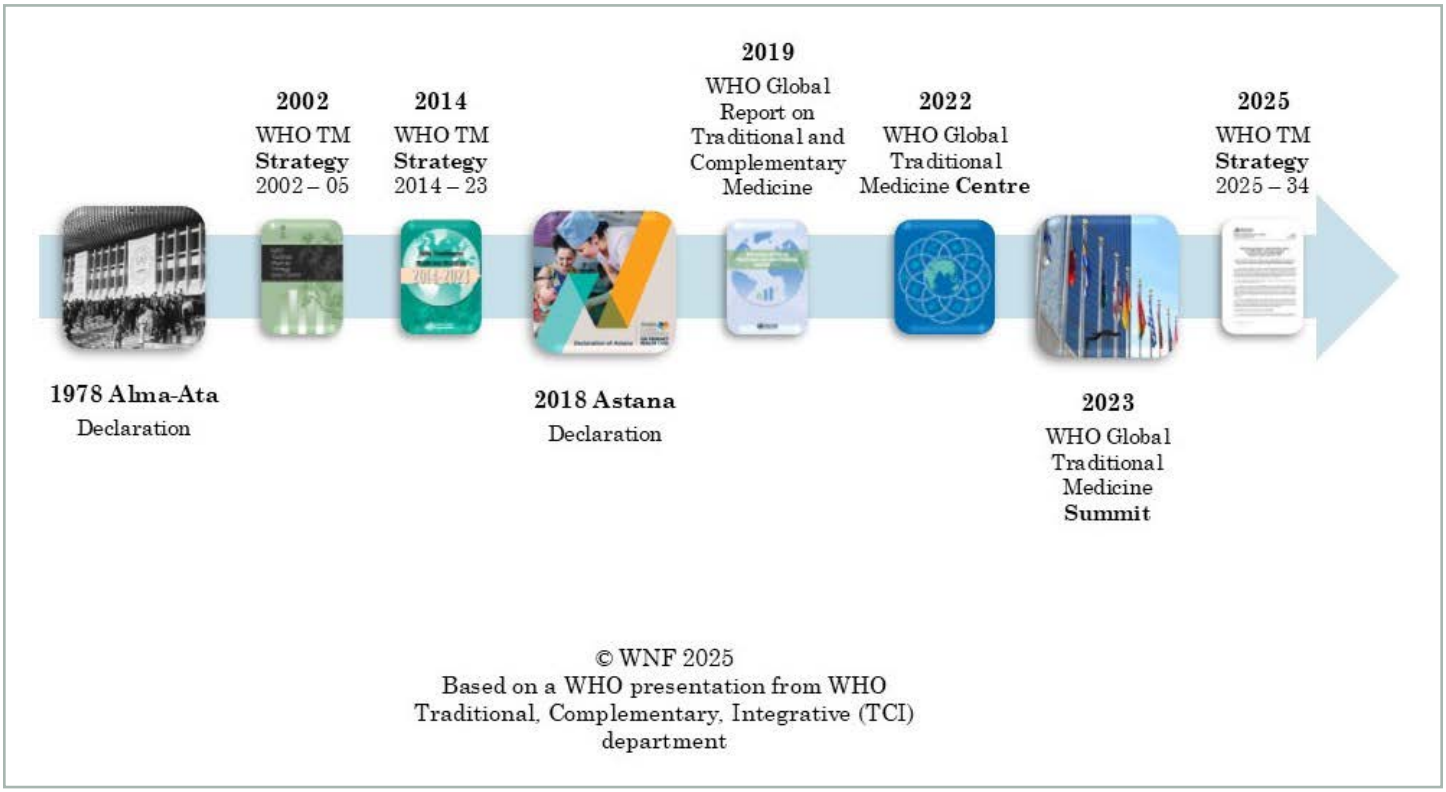

FIGURE 1 The WHO's Expedition into Traditional Medicine

2002–2005,[6] the second for 2014–2023,[7] and the current one for 2025–2034[8]. As outlined in Table 1, all include strategic objectives on policy and regulation; safety, efficacy and quality; and access to TM systems of medicine, including Chinese medicine, Ayurveda, Unani, naturopathy, osteopathy, homeopathy, chiropractic and others.[6,7,8] The Strategies outline strategic actions for member states, partners and stakeholders and the WHO. The WHO strategic actions focus on technical documents to support TM, education on TM, collaboration and dissemination of TM data.[6,7,8]

The 2002–2005 Strategy provided an overview of the global landscape for TM, the role of the WHO, a listing of international and national resources for TM and a call for member states to regulate TM products, practices and practitioners.[6] The 2014–2023 Strategy, published almost 10 years later, provided a global progress report and review of traditional and complementary medicine (T&CM) with a focus on policy and regulations as it related to TM products, practices, education, and research and the use and integration of T&CM.[7]

The 2014–2023 Strategy outlined the growing global demand and use of T&CM and stated that there had been significant progress in the number of member states with a TM policy and those regulating herbal medicines, as well as an increase in TM educational standards.[7] The report highlighted that there were still challenges related to development and enforcement of regulations, integration of TM into PHC, advertising challenges of T&CM, lack of funding and advancement in research and development, ability to assess the safety and quality of T&CM products and services, diversity in education and training, and ability to obtain reliable objective information on TM.[7] A 2019 interim report detailed the progress on many fronts and provided additional details by individual TM professions and by WHO regions.[9]

The progress outlined included:[7,9]

- The number of member states with a TM policy increased from 29 in 1999 to 69 in 2012 and 98 in 2018.
- The number of member states with a TM/CM research institute increased from 19 to 73 to 75, in the same time period.

A challenge outlined in the 2014–2023 Strategy included obtaining reliable information from member states. For example, the interim report indicates that 98 member states reported the use of naturopathy, with 9 regulating its practice, yet when compiling the Health Technology Assessment on Naturopathy, the WNF found that 108 countries have a naturopathic workforce, and of those, 34 countries regulate naturopathy.[10] Part of the challenge for TM professions such as naturopathy is that the Strategies report on national standards, yet some countries, such as Canada and the United States, regulate healthcare professions by province or state and regulate natural health products and herbal medicines nationally.[10]

The current WHO TM Strategy 2025–2034 was adopted at the Seventy-eighth World Health Assembly in May 2025.[8] The reach of this Strategy is significantly broader as it includes the three common strategic objectives as well as *evidence-based* and *cross-sector collaboration* (see Table 1). The guiding principles are more expansive and include a focus on holism and health,

TABLE 1 Strategic Objectives of the WHO Traditional Strategies

Strategic Objectives (SO)	2002–2005 Strategy	2014–2023 Strategy	2025–2034 Strategy
Policy and Regulation	Develop policies and programs that focus on integrating TM/CAM into national healthcare systems.	Build the knowledge base for active management of T&CM through appropriate national policies.	Support the provision of safe and effective TCIM through appropriate regulatory mechanisms
Safety, Efficacy and Quality	Encourage regulation and quality assurance standards that would ensure the safety, efficacy and quality of TM products and practices.	Strengthen the quality assurance, safety, proper use and effectiveness of T&CM by regulating products, practices, and practitioners.	Part of Policy and Regulation and Access and Integration SO
Access and Integration	Focus on accessibility and affordability of TM/CAM, with a specific focus on poor populations.	To promote UHC by integrating T&CM services into healthcare service delivery and self-health care.	Integrate safe and effective TCIM into health systems
Rational Use	Promote therapeutically sound use of appropriate TM/CAM by providers and consumers.	N/A	N/A
Evidence Base	N/A	N/A	Strengthen the evidence base on TCIM
Cross-sector Collaboration	N/A	N/A	Optimize the cross-sector value of TCIM and empower communities

TM/CAM: traditional medicine/complementary and alternative medicine; T&CM: traditional and complementary medicine; TCIM: traditional, complementary and integrative medicine; UHC: universal health care; N/A: not available.

sustainability and biodiversity, the right to health and autonomy, Indigenous Peoples' rights, culture and health, people-centred and community engagement, and integrated health services and health equity.[8] The increased breadth of the 2025–2034 Strategy demands that TM professions, such as naturopathy, maintain strong professional stewardship while actively looking for governmental, interprofessional, and interorganizational activities that have the potential to impact the profession, from the perspective of both risk and opportunity. Active engagement is required to ensure that the integrity, foundation, and complexity of naturopathy, from a research or educational perspective or as a healthcare delivery model, are protected and respected and that all aspects of collaborative integration allow for naturopathic care to remain true to its principles and theories, and maintain the breadth of naturopathic therapies and practices.

Some of the aspects of the 2025–2034 Strategy that could significantly impact the naturopathic profession include the ever-changing TM definitions, the lack of inclusion of professions, the research demands, and the lack of clarity around TM education.

Definitions of TM, CM, integrative medicine (IM), and combinations of the above continue to be a challenge for the WHO, as indicated in the changes in definitions in each Strategy.[6,7,8] It is likely that changes in the definitions are partly reflective of the increasing knowledge and awareness of the vast and variable field of T&CM. Separating non-codified and codified *systems of medicine* and distinguishing between systems of medicine and practices or assessment tools would help to clarify the definitions. For instance, traditional, Indigenous, complementary and integrative medicine (TICIM) should be adopted, with traditional used to reflect codified systems of medicine that include assessment, diagnosis and treatment (such as Ayurveda, Chinese medicine, naturopathy, etc.), Indigenous to reflect the breadth of all aspect of Indigenous medicines and people, complementary to reflect the range of traditional assessment-based tools (such as iridology or zone therapy) and the vast number of treatment-based practices (such as reiki or aromatherapy), and integrative to reflect conventional healthcare practitioners who are incorporating complementary practices or products. Needless to say, the discussion on definitions requires much more attention.

All Strategies focus on the regulation of TM products, practices and practitioners.[6,7,8] This is known as the 3 Ps. This approach does not include professions. Codified TM professions, such as naturopathy, are more than just a collection of products and practices. They have a defined educational structure that is based on a foundation of philosophies and principles, with an individualized approach to assessment, naturopathic diagnosis, and treatment.[10] Naturopathic care involves practitioners using a diverse range of lifestyle modifications and education, as well as therapeutic products and practices based on specific theories and approaches.[10] The lack of recognition and appreciation for the essential stewardship role that professions and professional associations undertake is a real concern. Whether the strategic objectives outlined in the 2025–2034 Strategy are an opportunity or a threat to TM professions depends on the degree to which TM professions are respected and included in the implementation at every level. Without recognition of TM professions, there is always the risk of practices and products being co-opted by other healthcare practitioners without the understanding that how the products and practices are applied determines their effectiveness. Professional stewardship is required to ensure that knowledge is appropriately codified, researched, and protected and that integrative health care is respectful and reflective of the foundational basis of every profession. From a WNF perspective, there are 4 Ps that need to be recognized, with professions being paramount.

Although there was recognition in the interim report and in the 2025–2034 Strategy that the funding and focus on TM research has been lacking over the years, the emphasis on research is emphatically woven throughout all aspects of the 2025–2034 Strategy, with a clear directive to member states to *only* regulate TM practices and products that are supported by research.[8] Although the

naturopathic profession embraces the focus on research, there are numerous hurdles that are foreseeable based on the Strategy:

- There is almost no recognition of the presence or research value of traditional knowledge. For TM professions that pre-date research, this is a significant concern.
- It is important to keep in mind that research paradigms that adequately evaluate complex TM systems have only gained attention in the last 20 years and have only recently started to be recognized as the preferred methods for assessing the effectiveness of TM systems.[11,12]
- The current research directive encourages the assessment of TM by individual practices and products instead of as a whole integrated profession, which threatens every aspect of TM.
- Although the Strategies acknowledge the lack of external commitment to funding and publishing of TM research, the 2025–2034 Strategy encourages the evaluation of TM based almost solely on research without the recognition that any gap or lack in research may be due to a lack of research funding and focus rather than a lack of efficacy or cost-effectiveness.

The naturopathic profession has demonstrated a continual commitment to research as outlined in the bibliometric analysis of naturopathic research,[13] the Health Technology Assessment on Naturopathy,[14] and the WNF's commitment to initiatives that focus on building global naturopathic research capacity.[1] That being said, the research directives in the 2025–2034 are potentially a threat to the naturopathic profession due to the focus on products and practices rather than on professions.

In addition to the focus on regulation of the 3 Ps and the emphasis on research, the 2025–2034 Strategy emphasizes the importance of educational standards and integrative educational curricula with other traditional, complementary, and integrative medicine (TCIM) professions and with conventional medicine, and it encourages integrative delivery of health care.[8] Cross-training and collaboration among TCIM professions and practices along with biomedicine may have its advantages as long as the difference between the educational requirements for familiarization, awareness and respectful collaboration and the education and training necessary to ensure competency as a practitioner or for a specific profession is clearly articulated. Another reason to recognize the need for professional stewardship.

CONCLUSION

The exponential rate of consumer engagement with TM, along with the rise of non-communicable diseases and other global health challenges, has captured the WHO's and member states' awareness, intrigue, suspicion, and caution of TM globally. This has resulted in a new level of both hope and scrutiny for TM from many different vantage points, especially research, education, and collaborative health care. The WHO's expedition into TM has brought to light many challenges both for TM professions and for the WHO and member states, especially as it relates to professional stewardship, realistic research demands, and respectful educational considerations.

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