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Curcumin and cancer: barriers to obtaining a health claim

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Curcumin is a highly pleiotropic molecule found in the rhizomes of Curcuma longa *(turmeric). It is responsible for the yellow color of turmeric and has been shown to inhibit the proliferation of cancer cells and to be of use in preventing or treating a number of diseases. Curcumin has been shown to modulate multiple cell-signaling pathways simultaneously, thereby mitigating or preventing many different types of cancers, including multiple myeloma and colorectal, pancreatic, breast, prostate, lung, head, and neck cancers, in both animal models and humans. Current therapeutic approaches using a single cancer drug for a single target can be expensive, have serious side effects, or both. Consequently, new approaches to the treatment and prevention of cancer, including the integration of curcumin as a viable treatment strategy where dysregulation of many pathways is involved, are warranted. A methodical review of the evidence was performed to evaluate the effects of curcumin in support of a health claim, as established through the regulatory framework of Health Canada, for a relationship between the consumption of curcumin and the prevention and treatment of cancer.*

INTRODUCTION

Curcumin is the bright-yellow-colored hydrophobic polyphenol present in the rhizome of turmeric (*Curcuma longa*), a perennial herb in the family *Zingiberaceae*.[1] Turmeric is traditionally used in many South Asian countries for a variety of purposes, including medicinal applications, food flavoring, and fabric coloring.[2] Curcumin has been used for over 2000 years as a traditional medicine in China and India.[3] Ayurveda, an ancient medical system followed in India, describes turmeric as a remedy to dress wounds and to treat skin diseases, eye infections, burns, bites, and acne.[2] Approximately 2–6% (wt/wt) of turmeric powder is curcuminoids, containing mostly curcumin, <20% demethoxycurcumin, and about 2% bis-demethoxy curcumin.[4] Although more than 300 other bioactive compounds have been isolated from turmeric,[5] including some essential oils,[4] curcumin has shown the greatest bioactivity. The beneficial health effects of curcumin are thought to be due to its anticarcinogenic,[1,4,6] antioxidant,[7,8] antimicrobial,[9–12] anti-inflammatory,[7,13] hepatoprotective and renoprotective,[14–16] and hypoglycemic effects.[17–19]

Despite the rich history and proven efficacious medicinal properties of curcumin, there is currently no approved health claim for this polyphenol. The objective of this review is to examine the medicinal properties of curcumin and to summarize the factors preventing a health claim for this curcuminoid. Using Health Canada as a model regulatory jurisdiction, studies on the health-promoting effects of curcumin, particularly its antineoplastic effects, are assessed against a number of criteria stipulated by this regulatory body. Thus, the specific aims of this review are as follows: 1) to review the current regulatory framework in Canada for

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allowing health claims to appear on food labels, and 2) to evaluate the available clinical evidence of the anticancer properties of curcumin by using Health Canada's criteria for evaluating a health claim submission.

CURCUMIN AND CANCER

Although curcumin has been shown to exhibit beneficial effects in many diseases, its effect on cancer has been studied the most. Cancer is characterized by an increase in the rate of cell proliferation, which results from genetic and epigenetic mutations as well as a disrupted cell cycle.[4] Cancer involves the dysregulation of multiple cellular pathways that normally regulate cell proliferation. The annual global incidence of cancer is expected to increase from 14.1 million new cases in 2012, with 8.2 million deaths, to nearly 25 million in 2032.[20] The ability of curcumin to target multiple pathways makes it an extremely potent anticancer agent. Curcumin, alone or in combination with other agents, has been used for the prevention and treatment of various forms of cancer in humans, including colorectal cancer,[21,22] pancreatic cancer,[23] breast cancer,[24,25] prostate cancer,[26] multiple myeloma,[25] lung cancer, and oral cancer.[25] The potent antineoplastic properties of curcumin against such a wide range of cancers are thought to be accomplished through proapoptotic, antiproliferative, antioxidant, and anti-inflammatory mechanisms.[27–29] As a pleiotropic molecule, curcumin has the ability to affect multiple signaling pathways simultaneously by inhibiting cell proliferation and enhancing apoptosis. Shehzad and Lee[30] have provided a detailed account of the role of curcumin in modulating the apoptotic signaling cascade, the protein p53 (p53) signaling pathway, the nuclear factor-κB (NF-κB) pathway, the mitogen-activated protein kinase (MAPK) pathway, the Akt pathway, the Notch-1 signaling pathway, the nuclear factor-like 2 (Nrf2) pathway, the Wnt/β-catenin signaling pathway, the Janus kinase/signal transducers and activators of transcription (JAK/STAT) signaling pathway, the AMP-activated protein kinase/cyclooxygenase 2 (AMPK/COX-2) pathway, and other targets. Molecular targets of curcumin in cancer are listed in Table 1.[4,31–40] Mechanistically, the structure of curcumin possesses a high level of methoxylation and a low level of hydrogenation, which together have been shown to enhance the scavenging of free radicals; thus, the anticancer, antioxidant, and anti-inflammatory effects of curcumin may be attributed in part to these structural properties.[41–43]

Curcumin's role in cancer as a natural antioxidant agent remains controversial. While natural antioxidants are widely expected to be beneficial to cancer patients undergoing treatment, results from a number of clinical trials have indicated otherwise.[44] To be clear, the intake of dietary or natural antioxidants before cancer diagnosis is widely claimed to be highly effective in preventing cancer and/or in increasing survival rates in cancer patients.[45–47] The modulation of antioxidant and free-radical activity is a complex biochemical and physiological interaction that has limited semblance to observations during in vitro experiments[44]; thus, the outcome of the use of natural or dietary antioxidants by cancer patients undergoing treatment can be described as uncertain, at best. For instance, although certain studies report a reduced risk of mortality following dietary intake of antioxidants and/or supplementation with antioxidants in cancer patients,[45,48] others suggest that the use of antioxidants may indeed be inimical to cancer subjects.[49,50] Additionally, high doses of antioxidants have been correlated with attenuated growth of cancer cells and no adverse consequences for normal cells,[51,52] while moderate doses of natural antioxidants have been demonstrated to reduce the efficacy of radiation treatments in cancer patients.[53,54] These results raise the questions of if, how, and to what extent natural antioxidants could be used and relied upon by cancer patients. Current thinking on cancer biology and redox therapy suggests the development of antioxidant treatment regimens that aim to directly inhibit the production of reactive oxygen species (ROS) generated by mitochondrial respiration or NADPH oxidases or to scavenge ROS at their sites of production within the cell,[55] since it has been shown that antioxidants targeted at the mitochondria are more effective at inhibiting the proliferation of tumor cells than the same antioxidants when present in the cytosol,[56] a finding attributed to the poor interaction of cytosolic antioxidants with the ROS localized in the mitochondria.[55] Recently, it has been proposed that curcumin's ability to induce apoptosis in cancer cells is possibly through a mitochondrial-mediated pathway.[57] To this end, a health claim for curcumin-based treatment strategies or natural health products could very well be timely.

Curcumin nutritional supplements are currently available worldwide[25] and rank among the most popular nutritional supplements on the US market, with sales of curcumin and turmeric-based supplements expected to grow by >21% by 2016.[58,59] In Canada, curcumin has gained status as a natural health product,[60] and two statements have been approved to appear on the packaging of supplements: 1) "Provides antioxidants for the maintenance of good health," and 2) "Used in herbal medicine to help relieve joint inflammation."[60] Despite the rich history and proven efficacious medicinal properties of curcumin, there is currently no approved health claim regarding the antineoplastic effects of this polyphenol.

Table 1 **Effect of curcumin alone or in combination on molecular targets of cancer treatment.**

Type of cancer	Molecular targets of curcumin
Prostate cancer[31]	↑ (Bcl-2 L1, Bcl-2 L11, BAK1, BAX, BBC3, PMAIP 1, p53 protein) ↓(NFKBIA, AKT 1, Bcl-2, BIRC4, BIRC5, PTEN, NKX 3A, CSF 1R, EGFR, NF-κB) ↑↓ (caspase-3, caspase-8)
Pancreatic cancer[32,33]	↑ (caspase-3, PARP, P-ERK1/2, c-Jun protein, p38 MAPK, p53 protein, miR-200) ↓ (NF-κB, cyclin-D1, c-myc protein, Bcl-2, Bcl-xL, cIAP-1,MMP, COX-2, VEGF, Sp-1, Sp-3, Sp-4, survivin, VEGF, PGE_2, miR-21)
Colorectal cancer[4,34,35]	↑ (DR-5, IGF-1R, IGFBP-3) ↓ (COX-2, NF-κB, Bcl-2, Bcl-xL, cyclin D1, c-myc, VEGF, IL-8, MMP-9, PGE_2) ↑↓ (EGFR)
Breast cancer[4,36,37]	↑ (TIMP-1, p21, p27) ↓ (NF-κB, AP-1, COX-1, COX-2, VEGF, FGF, cyclin E, IL-6, IL-11, TGF-β, MMP-2, MMP-9, MMP-13)
Multiple myeloma[4]	↑(caspase-7, caspase-9, PARP) ↓(IkBα, Bcl2, Bcl-xL, cyclin D1, IL-6, COX-2, NF-κB)
Leukemia[38–40]	↑(BAX, caspase-3, caspase-8, p21, p27) ↓(Bcl-2, PARP, cyclin D3, STAT3, AKT, NF-κB, Mcl-1, XIAP)

Abbreviations: AKT, protein kinase B; AP-1, activator protein 1; BAK, Bcl-2 homologous antagonist/killer; BAX, Bcl-2-associated X protein; BBC3, Bcl-2-binding component 3; Bcl-2, B-cell lymphoma 2 protein; Bcl-xL, X-linked inhibitor of Bcl; BIRC, Baculoviral inhibitors of apoptosis repeat containing protein; cIAP-1, cellular inhibitor of apoptosis protein-1; COX-1, cyclooxygenase 1; COX-2, cyclooxygenase 2; CSF 1R, colony stimulating factor 1 receptor; DR-5, a tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) receptor; EGFR, EGF-receptor; FGF, fibroblast growth factor; IL, interleukin; IGF-1R, insulin like-growth factor (IGF)-1-receptor; IGFBP-3, IGF-binding protein 3; IkBα, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha; MAPK, mitogen-activated protein kinase; miR, microRNA; MMP, matrix metalloproteinase; Mcl-1, myeloid cell leukemia 1; NF- κB, nuclear factor-κB; NFKBIA, nuclear factor (NF)-κB inhibitor alpha; NKX 3A, a homeodomain-containing transcription factor; PARP, poly(ADP-ribose) polymerase (PARP) proteins; P-ERK1/2, phospho extracellular signal-regulated kinase 1/2; PGE_2: prostaglandin E_2; PMAIP 1, phorbol-12-myristate-13-acetate-induced protein 1; PTEN, phosphatase and tensin homolog; Sp, specificity protein; STAT3, signal transducer and activator of transcription 3; TGF-β, transforming growth factor-β; TIMP-1, tissue inhibitor of metalloproteinase-1; VEGF, vascular endothelial growth factor; XIAP, X-linked inhibitor of apoptosis protein.

BIOAVAILABILITY

Curcumin has limited bioavailability because it is poorly absorbed, rapidly metabolized, and systemically eliminated.[61] These characteristics are among several barriers to its use as a therapeutic agent. Various approaches have been adopted to improve the bioavailability of curcumin, including the use of liposomal curcumin, curcumin nanoparticles, phospholipid complexes, and structural analogs as well as the use of piperine as an adjuvant.[61] Other widely researched strategies for increasing bioavailability are the blocking of metabolic pathways by route and medium of administration, by structural modifications, and by simultaneous administration of other agents, although none of these has produced evidence of significant overall improvement.[62] Nevertheless, a nanoparticle-based preparation of curcumin was recently reported to result in 27-fold higher blood levels in humans compared with curcumin powder,[63] which indicates its use could serve as a promising therapeutic strategy. The bioavailabilities of different curcumin formulations in humans and animals are listed in Table 2.[63–74]

TOXICITY AND FEASIBILITY OF CONSUMPTION

The consumption of curcumin is generally considered safe, a conclusion based largely on the long history of curcumin use in South Asian countries. Dose-escalating studies have demonstrated the safety of consuming up to 12 g of curcumin per day, with no detrimental effects.[75] In fact, beneficial effects of curcumin on cancer were shown with intakes ranging from 100 mg/d to 6 g/d in human clinical trials, with most studies showing benefits at dosages of around 2–3 g/d (see Table 3[21,26,78–80] for a list of human clinical studies selected for review, as described in the "Methodology" section below). Moreover, if increased bioavailability is attained, lower quantities of curcumin may be sufficient to produce positive effects.

Additionally, several concerns about the correlation of curcumin intake with the inhibition of certain drug-metabolizing enzymes,[81] with potential DNA damage,[82] and with iron chelation have been raised.[83] However, further research is required to clarify the relationship between possible DNA damage and curcumin, since some reports suggest the prevention of DNA damage by curcumin.[84,85] On the other hand, curcumin's reported role in the chelation of iron could indeed be beneficial, since excess iron in cancer cells is thought to promote their proliferation. Nevertheless, there are still concerns about the reported chelation of iron by curcumin, especially in cancer patients with marginal iron stores and in certain categories of female cancer patients who have reduced iron levels due to blood loss during child birth or menstruation.[86] Ultimately, the optimal strategy to avail the ability of curcumin to chelate iron and to inhibit certain important enzymes could lie in targeted polytherapy, since cancer formation involves multiple signaling pathways.[87]

TURMERIC VERSUS CURCUMIN

Although curcumin is the major bioactive agent in turmeric, some research suggests that certain activities of turmeric are independent of curcumin.[25] In mice[88] and

Table 2 **Oral bioavailability of various curcumin formulations.**

Reference	Preparation	Subject	Oral bioavailability compared with that of curcumin
Yang et al. (2007)[64]	Pure curcumin	Rats	1%
Khalil et al. (2013)[65]	PLGA and PLGA-PEG blend nanoparticles with curcumin	Rats	15.6- and 55.4-fold higher
Takahashi et al. (2009)[66]	Liposome-encapsulated curcumin	Rats	4.96-fold higher
Sharma et al. (2010)[67]	Piperine coadministration with curcumin	Rats	20-fold higher
Liu et al. (2006)[68]	Phospholipid complex of curcumin	Rats	3.4-fold higher
Yu et al. (2012)[69]	Nanoemulsion of curcumin with polysorbate	Mice	9-fold higher
Hu et al. (2012)[70]	Curcumin microemulsion with Capryol 90, Cremophor RH40, and Transcutol P	Rats	22.6-fold higher
Shoba et al. (1998)[71]	Piperine coadministration with curcumin	Rats	1.54-fold higher
		Humans	20-fold higher
Sasaki et al. (2011)[63]	Theracurmin (curcumin dispersed with colloidal nanoparticles)	Humans	27-fold higher
Antony et al. (2008)[72]	Biocurcumax: combination of curcuminoids and volatile oils of turmeric rhizome	Humans	6.93-fold higher
Cuomo et al. (2011)[73]	Meriva: lecithin formulation of curcuminoid mixture	Humans	29-fold higher
Jäger et al. (2014)[74]	Curcumin phytosome formulation	Humans	7.9-fold higher
	Curcumin formulation with volatile oils of turmeric rhizome		1.3-fold higher
	Curcumin formulation with hydrophilic carrier, cellulosic derivatives, and antioxidants		45.9-fold higher

Abbreviations: PLGA, polylactic-co-glycolic acid; PLGA-PEG, PLGA-polyethylene glycol.

rats,[89] curcumin-free turmeric extracts were shown to inhibit tumorigenesis induced by various agents. Cell culture studies have also demonstrated curcumin alone to have less potency in suppressing cancer growth than turmeric containing similar amounts of curcumin.[90] Furthermore, studies in animal models demonstrated superior ability of whole turmeric over curcumin in reducing diabetic cataracts and blood glucose levels.[91,92] Together, these studies suggest that the synergistic effects of other bioactive components in turmeric might translate to greater potential in therapeutic use; however, these findings have yet to be replicated in humans.

REGULATORY FRAMEWORK FOR HEALTH CLAIMS IN CANADA

Health Canada defines a health claim as "any representation on labelling or advertising that states, suggests or implies that a relationship exists between consumption of a food or an ingredient and a person's health." According to the Food and Drugs Act, the Food and Drug Regulations, and the Natural Health Products Regulations, Health Canada is responsible for developing policies, regulations, and standards relating to health and safety aspects of food.[93] The role of the Canadian Food Inspection Agency is to ensure compliance and enforcement of those standards.[93] The current regulatory framework employed by Health Canada allows four types of health claims to be made on labeling and in advertising, including disease risk reduction claims, structure function claims, nutrient function claims (biological role claims), and probiotic claims.[94] A disease risk reduction claim highlights 1) a "specific relationship between a food, a food constituent, or the characteristics of a diet and a reduced risk of developing a diet-related disease or condition" or 2) a "therapeutic effect of a food, food constituent or diet, including restoring, correcting, or modifying body functions."[94] Disease risk reduction claims require premarket approval from Health Canada. Structure function claims and nutrient function claims are statements based on the "specific beneficial effects that the consumption of a food or a food constituent has on the normal functions or biological activities of the body."[94] Although these function claims do not require preapproval, companies are required to submit the evidence to the Canadian Food Inspection Agency upon request. Probiotic claims are allowed on products that contain "live microorganisms which when administered in adequate amounts confer a health benefit on the host." Eligible bacterial species for this type of claim are defined in Table 8.4 of Health Canada's *Guide to Food Labelling and Advertising*.[94]

Disease risk reduction claims have the greatest impact on the marketing of the product and on the health of the consumer. Principles and procedures that are to be followed for health claim submissions are explained in detail in Health Canada's *Guidance Documents for Preparing Health Claim Submissions*.[77] This guide ensures "that health claims for foods are substantiated in a systematic, comprehensive and transparent manner."[77] In short, every submission should follow 13 well-described steps that aim to bring a totality of evidence to the discussion, to assess the quality of the studies, and to determine causality, consistency, and minimum effective dose of the product. The petition is then concluded on the basis of the above results and the "generalizability of the data to the target population, physiological meaningfulness, and feasibility of consuming an effective amount of the food" (Figure 1).

Table 3 **Selected human clinical trials for assessing causality, effect, direction, and scientific agreement.**

Reference	Study quality score[a]		Type of cancer	No. of participants	Duration of trial	Compound and daily dose	Other simultaneous treatments	Side effects	Results ($P \leq 0.05$)
	Jew et al.[76]	Health Canada[77]							
Ryan et al. (2013)[78]	**** +	12	Noninflammatory breast cancer	30	7 wk	6 g curcumin (C3 complex capsules)	Radiation therapy	None	Reduced radiation dermatitis Reduced moist desquamation No change in redness and pain
Golombick et al. (2012)[79]	**** Φ	10	Myeloma precursors (MGUS & SMM)	36	3 mo	4 g curcumin (one C3 curcuminoid granule stick-pack [Alleppey finger turmeric] per day)	None	Diarrhea	No change in FLC assay No change in uDPYD (born turnover) Decreased urinary protein
Ghalaut et al. (2012)[80]	** Φ	6	Chronic myeloid leukemia	50	6 wk	15 g turmeric powder (5 g dissolved in 150 mL of milk, 3 times per day)	Imatinib therapy	Gastritis, skin pigmentation, arthralgia, edema	Marked reductions in NO levels
He et al. (2011)[21]	*** +	11	Colorectal cancer	126	10–30 d	1.08 g curcumin (360-mg capsule, 3 times per day)	None	Diarrhea	Improved body weight Reduced TNF-α Increased apoptosis of tumor cells Reduced DNA fragmentation Enhanced p53 activity
Ide et al. (2010)[26]	**** +	11	Increased PSA	100	6 mo	100 mg curcumin (tablets)	Soy isoflavones (40 mg)	None	No change in PSA Subset of subjects with initial PSA ≥10 ng/mL had a decrease in PSA

Abbreviations: C3 complex, curcumin (∼80–90%) + demethoxy curcumin (∼8–15%) + bis demethoxy curcumin (∼2–2.5%); FLC, free light chain; MGUS, monoclonal gammopathy of undetermined significance; NO, nitric oxide; PSA, prostate-specific antigen; SMM, smoldering multiple myeloma; TNF-α, tumor necrosis factor α; uDPYD, deoxypyridinoline.
[a]Grading system outlined in *Guidance Document for Preparing a Submission for Food Health Claims*[77] and Jew et al.[76]

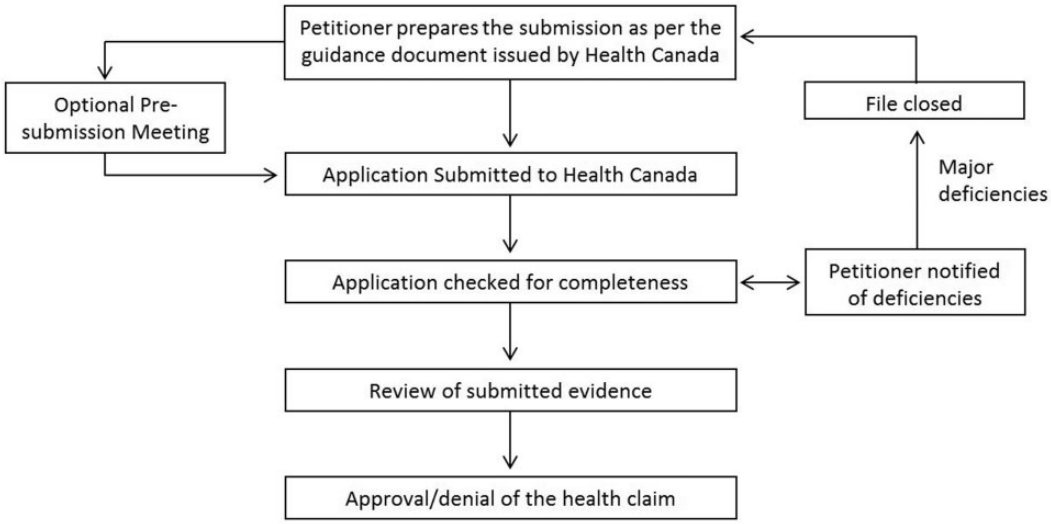

Figure 1 **Procedure followed by Health Canada in approving a health claim application.**

The principles followed in granting a health claim are generally robust, although the tools to evaluate study quality appear to be suboptimal. The current criteria allocate equal weight for actual study design parameters (e.g., randomized, blinded) and manuscript parameters (e.g., reported dropouts, and type and amount of food described). This might result in a poorly designed study receiving a higher score because of proper reporting.

Another major concern with the current regulatory system is the lack of clarity in whether to classify a bioactive compound either as a food or as a natural health product. The guidance document from Health Canada for the classification of products at the food/natural-health-product interface[95] is insufficient in categorizing many bioactive compounds. Under the current set of guidelines, obtaining a health claim through the Natural Health Products Regulations framework appears far easier than doing so through the Food and Drug Regulations framework, as evidenced by the more than 70,000 natural health product claims approved[96]; in contrast, only 11 disease risk reduction or therapeutic claims for foods are currently accepted by Health Canada.[97] However, the general lack of clarity about health claims[93] may lead the consumer to consider a health claim on a natural health product label to be equally scientifically robust as one on a food label.

CURCUMIN AND CANCER: HEALTH CLAIM ASSESSMENT

Methodology Combinations of the search words "curcumin," "cancer," "carcinoma," and "myeloma" were used to retrieve publications in English with one or more of these words in their title, abstract, or subject headings from the PubMed database. Out of 2,365 publications, 32 were clinical trials conducted in humans. A search in the Cochrane Library database with the same search words retrieved 7 clinical trials, 5 of which were duplicates from PubMed and 2 of which were poster presentations. Inclusion and exclusion criteria were applied to the above 32 studies from the PubMed and Cochrane Library databases. Studies conducted in human subjects that included effects on cancer markers as primary or secondary outcome measures were included. Studies without a control group, curcumin/turmeric administration, or a cancer outcome measurement were excluded. Twenty studies were excluded because they were categorized as any of the following: human cell culture studies; case studies; field trials; studies measuring pharmacokinetics, pharmacodynamics, bioavailability, absorption, tissue levels, or safety; or studies in which curcumin was not administered. Seven human studies that measured cancer outcomes were excluded (Table 4[22,98–103]) because they did not have a control group; most of these were dose-escalation and toxicity studies, case studies/patient reports, or field trials. In addition, these 7 studies received a "lower quality study" rating ($\leq$7 points) using Health Canada's quality appraisal tool for intervention studies, potentially rendering them irrelevant and unusable in Health Canada's decision-making process. It is hoped that this review will communicate to researchers that poorly designed studies (such as those without control groups) have a diminished potential for use in such important policy decisions as health claim approvals. Only 5 studies met the inclusion criteria and were selected for evaluation of study quality and assessment of causality, effect direction, and scientific agreement (Table 3). Health Canada's quality appraisal tool for intervention studies was used to evaluate the study quality. In addition, another tool developed by Jew et al.[76] for comparing

Table 4 **Human studies excluded due to lack of a control group.**

Reference	Study quality score (Health Canada[93])	Type of cancer	No. of participants	Duration of study	Compound and daily dose	Other simultaneous treatments	Side effects	Results
Bayet-Robert et al. (2010)[98]	4	Advanced or metastatic breast cancer	13	6 wk	Dose escalation, 0.5–8 g curcumin (capsules)	Docetaxel	Diarrhea, neutropenia	Recommended dose of curcumin set at 6 g/d (with docetaxel). Dose level of curcumin had no effect tumor markers
Epelbaum et al. (2010)[99]	7	Adenocarcinoma of the pancreas	11	1 wk to 12 mo	8 g or 4 g curcumin (capsules)	Gemcitabine	Gastrointestinal toxicity	Local control and survival results showed efficacy comparable with that of gemcitabine alone
Dhillon et al. (2008)[100]	4	Adenocarcinoma of the pancreas	21	8 wk	8 g curcumin (C3 capsules)	None	No treatment-related toxic effects	Established tolerability of 8 g/d curcumin
Carroll et al. (2011)[22]	5	Patients referred for screening colonoscopy or sigmoidoscopy	41	30 d	2 g or 4 g curcumin (>98% pure curcumin powder, capsules)	None	Gastrointestinal disturbances	No change in 5-HETE, PGE_2, or proliferation. 4 g, but not 2 g, decreased rectal ACF
Cruz-Correa et al. (2006)[101]	5	Familial adenomatous polyposis	5	6 mo	1.44 g curcumin (480 mg, 3 times per day)	Quercetin	Nausea, sour taste, and loose stools	Decreased polyp number and size from baseline
Garcea et al. (2005)[102]	6	Colorectal cancer	12	7 d	3.6 g, 1.8 g, or 0.45 g curcumin (C3 capsules)	None	Not reported	3.6 g curcumin reduced M_1G levels. No effect on COX-2 levels
Sharma et al. (2004)[103]	7	Colorectal cancer	15	Up to 4 mo	3.6 g, 1.8 g, 0.9 g, or 0.45 g curcumin (C3 capsules)	None	Nausea and diarrhea	3.6 g curcumin inhibited PGE_2 in blood leukocytes. No effect on M_1G levels or GST activity

Abbreviations: ACF: aberrant crypt foci; COX-2: cyclooxygenase 2; GST, glutathione S-transferase; 5-HETE, 5-hydroxyeicosatetraenoic acid; M_1G, 3-(2-deoxy-β-di-erythro-pentafuranosyl)-pyr[1,2-α]-purin-10(3H)one; PGE_2, prostaglandin E_2.

health claim regulatory systems across global jurisdictions was used to evaluate the quality of these studies for comparison with the results obtained using the Health Canada quality appraisal tool. In short, a 4-star system was used to rate the quality of the study design, and the following symbols were used to indicate key information that was missing in the report: +, Φ, and –.[76]

Study quality, causality, and effect direction Four studies[21,26,78,79] scored more than 8 points and were considered higher-quality studies by Health Canada's tools. One study[80] scored only 6 points due to failure to report the method of randomization, blinding, and attrition. Four studies that were considered higher-quality studies by Health Canada standards scored 4 stars and either a + or Φ status with the tool of Jew et al.[76] Thus, the quality ratings obtained in both systems were comparable. The system used by Jew et al.,[76] however, allows a distinction to be made between the quality of study design and the quality of reporting. The study characteristics, doses, and cancer-related outcomes from these 5 studies are shown in Table 3 and are discussed below.

Curcumin in the treatment of cancer Three of the selected studies investigated the role of curcumin in the treatment of cancer. Ryan et al.[78] examined the ability of oral curcumin to reduce the severity of radiation dermatitis in 30 patients receiving radiation therapy for breast cancer in a randomized, double-blind, placebo-controlled trial. Patients took four 500-mg curcumin or placebo capsules 3 times daily during their prescribed course of radiation therapy. Curcumin administration reduced radiation dermatitis severity and moist desquamation but not redness and pain. Although the results were encouraging, it is worth noting that curcumin affected the side effects of radiation therapy but not the markers of cancer itself. Ghalaut et al.[80] conducted a randomized study in 50 patients with chronic myeloid leukemia to determine the effect of turmeric powder on nitric oxide levels before and after imatinib therapy. Increased levels of nitric oxide have been found to cause tumorigenesis through mechanisms involving various protein kinases and transcription factors that cause DNA damage.[104] Administration of turmeric powder (15 g/d) resulted in higher reductions in nitric oxide levels compared with imatinib therapy. However, since patients were given turmeric, rather than curcumin, each day, it is not clear if the effects observed result from the curcumin in the turmeric or from other bioactive components in turmeric. He et al.[21] conducted a study in a group of colorectal cancer patients who received curcumin therapy (1.08 g/d) after diagnosis and before surgery. Tissue samples collected during biopsy and surgery were used for analysis. Curcumin administration during the waiting period for surgery (10–30 d) increased apoptotic tumor cells, enhanced expression of the p53 molecule in tumor tissue, modulated the tumor cell apoptotic pathway, decreased serum TNF-α levels, and improved body weight. It is noteworthy that all of the patients in the study were Chinese; thus, the probability for these effects to be replicated in other genetic cohorts should be confirmed.

Curcumin and cancer prevention Various tests in murine models have shown that curcumin has chemopreventive properties. For instance, curcumin was demonstrated to prevent cancer by significantly reducing the expression of cell proliferation biomarkers (5-bromo-2′-deoxyuridine labeling index) in a nonlesional esophageal epithelium, thus inhibiting *N*-nitrosomethylbenzylamine-activated esophageal carcinogenesis.[105] Additionally, curcumin at a dose of 0.2–0.5% of the normal diet was found to inhibit the proliferation of adenoma cells in the intestinal tract of a mice model of human familial adenomatous polyposis.[106] It has also been recently reported that curcumin is under investigation as a chemopreventive agent in human clinical trials.[107]

Two studies selected for evaluation examined the effect of curcumin in cancer prevention. Golombick et al.[79] conducted a randomized, double-blind, placebo-controlled crossover study of the effects of curcumin (4 g/d) on paraproteinemia, serum-free light chains, and bone turnover in patients with monoclonal gammopathy of undetermined significance and smoldering multiple myeloma. Monoclonal gammopathy of undetermined significance and smoldering multiple myeloma are asymptomatic plasma cell disorders with a potential to progress to multiple myeloma and are considered only precursors, and not myeloma. Curcumin therapy failed to show any significant benefit in either free light-chain assay or paraprotein levels. Deoxypyridinoline, a marker of bone resorption, was reduced in the curcumin arm and elevated in the placebo arm. Random protein levels in urine were reduced with curcumin administration. Ide et al.[26] studied the effects of soy isoflavone and curcumin on serum prostate-specific antigen (PSA) levels in men without detectable prostate cancer in a double-blind, placebo-controlled clinical trial. PSA levels were not affected by the treatment; however, a subset of subjects with an initial PSA level $\geq$10 ng/mL showed a decrease in PSA levels. It is difficult to assess if the benefits were from curcumin or from soy isoflavones, as the treatment was administered as a combination of the 2 bioactive compounds. Moreover, it is noteworthy that this study was conducted in Japanese men with increased PSA levels, with no confirmed cancer diagnosis.

Only 2 of the evaluated studies showed a benefit on specific cancer markers following curcumin administration: 1 study was conducted in a Chinese cohort,[21] and the other[80] was rated of low quality.

Scientific agreement outcome From the current set of data, which is based on limited research, it is difficult to confirm a positive role of curcumin in the prevention and treatment of cancer. As a result, it may prove difficult to obtain a health claim based on the current evidence. However, it is evident that more high-quality human clinical trials designed to study the effect of curcumin on cancer-specific markers are required to validate the benefits currently seen in animal models and cell culture studies.

In order to obtain an understanding of the current status of clinical trials in this field, the authors searched the clinical trials database of the US National Institutes of Health (www.clinicaltrials.gov) using the terms "curcumin" and "cancer." Forty-seven studies were retrieved in total. Eight of these studies have been either withdrawn or terminated, while the current statuses of 7 studies (started before July 2011) are shown as unknown. Whether the results from these studies were published is unclear. Eighteen other studies are shown as active, with most of them currently recruiting participants. Another 14 studies are shown as completed, 9 of which either have results available or were recently completed. However, 4 of the completed studies that were completed before 2010, as well as another 1 that was started in 2006 but has no completion date, are shown as "no study results posted." These results point towards a potential publication bias, although other reasons for a study termination are possible. New results from completed trials that have yet to be published might facilitate a health claim for curcumin in the near future.

CONCLUSION

Curcumin possesses great promise as a functional food ingredient in the prevention and treatment of various types of cancer. Although a considerable body of scientific evidence substantiates the positive correlation between curcumin consumption and a reduction in the risk of cancer, the paucity of suitably designed human clinical trials that clearly demonstrate any direct effect of curcumin on cancer markers may prevent Health Canada from approving a cancer risk reduction claim for curcumin within the current regulatory framework. Immediate research needs include additional human clinical trials and investigations of measures to improve the bioavailability of curcumin.

Although the prospect of using curcumin in cancer prevention and/or therapy seems promising, as with all other natural compounds, there are reasonable concerns regarding what would constitute an appropriate dosage, what resources and processes should be used for product standardization, and how clinical trials should be funded. As suggested in an earlier review, human clinical trials designed to assess natural antioxidants such as curcumin should be double blinded, randomized, and placebo controlled and should have clearly defined endpoints that include serum and tissue levels of curcumin.[44] Since curcumin-based interventions have been studied mainly in colon cancer, it would be sensible to begin with a pilot study involving that type of cancer in order to establish a suitable number of clinical trial subjects and thus avoid the so-called "beta error."[44] Finally, in designing clinical trials, care should be taken to distinguish between prevention-targeted and treatment-targeted trials. Prevention trials, in particular, should use a feasible dose (2–3 g/d) to evaluate the effects.

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