The Plausible Use of Mango (*Mangifera indica*) Peel Isoquercitrin as Adjuvant Therapy for Colorectal Cancer: Translating Research from Bench to Bedside

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ABSTRACT

A deadly and debilitating disease, colorectal cancer (CRC), is rapidly becoming a significant threat to public health. However, current therapeutic approaches are still hampered by various side effects. Due to its benefits and remarkable apoptotic impact on cancer cells, plant-derived flavonoids now garner interest as candidates for cancer therapy. Isoquercitrin, a flavonoid commonly found in fruit plants, especially mangoes, is notable due to its ability to inhibit cancer development through various mechanisms. This review aims to highlight the use of isoquercitrin extracted from mango peels in inhibiting CRC carcinogenesis. A literature search was done on Pubmed, Proquest, and Google Scholar using inclusion and exclusion criteria, and a narrative review was synthesised using the evidence gathered. Validity assessment was done through the Office of Health Assessment and Translation (OHAT) and Oxford Center for Evidence-Based Medicine (CEBM) critical assessment tools. Evidence suggested that isoquercitrin is promising as adjuvant therapy in CRC. It may inhibit overaccumulation of cytoplasmic β-catenin and its translocation into the nucleus, thus downregulating the expression of target proto-oncogenes leading to carcinogenesis of colon crypts. Isoquercitrin concentration in mango peel is abundant, 557.7 mg/kg in dried mango peel and 31.0 mg/kg in pure extracts. A pharmacology study approved that a daily intake of 5.4 mg/kgBW of isoquercitrin has an effective anticancer effect. This substance has good oral bioavailability and is well-tolerated but inhibits the metabolising enzymes CYP1A1 and CYP1B1. In conclusion, isoquercitrin is a potential adjuvant in inhibiting CRC growth with minimum costs and side effects.

Keywords: *colorectal cancer, herbal medicine, mango peel, adjuvant therapy, Wnt/β-catenin, isoquercitrin*

ABSTRAK

Kanker kolorektal (KKR) menjadi ancaman yang signifikan bagi kesehatan masyarakat karena sifatnya yang mematikan dan melemahkan. Meskipun demikian, pendekatan terapeutik saat ini masih terhambat oleh beragam efek samping terapi. Akibat dampak apoptotiknya yang kuat terhadap sel kanker, flavonoid yang berasal dari tumbuhan kini menarik perhatian sebagai kandidat untuk terapi kanker. Isokuersitrin, flavonoid yang berasal dari buah-buahan, terutama mangga, dikenal mampu menghambat karsinogenesis melalui berbagai mekanisme. Tinjauan ini bertujuan menyoroti penggunaan isokuersitrin dari kulit mangga dalam menghambat karsinogenesis KKR. Pencarian literatur dilakukan di Pubmed, Proquest, dan Google Scholar menggunakan kriteria inklusi dan eksklusi, dan narasi disintesis menggunakan bukti yang dikumpulkan. Penilaian validitas

dilakukan menggunakan alat bantu penilaian dari Office of Health Assessment and Translation (OHAT) dan Oxford Center for Evidence-Based Medicine (CEBM). Literatur menunjukkan bahwa isokuersitrin menjanjikan sebagai terapi adjuvan pada KKR, dan dapat menghambat akumulasi berlebih dari β-katenin sitoplasma dan translokasinya ke dalam nukleus, sehingga menurunkan regulasi ekspresi proto-onkogen yang mengarah pada karsinogenesis kripta kolon. Konsentrasi isokuersitrin pada kulit mangga cukup tinggi, 557,7 mg/kg pada kulit mangga kering dan 31,0 mg/kg pada ekstrak murni. Sebuah studi farmakologi menunjukkan bahwa asupan harian isokuersitrin 5,4 mg/kgBB memiliki efek antikanker yang efektif. Zat ini memiliki bioavailabilitas oral dan toleransi yang baik tetapi dapat menghambat enzim metabolisme CYP1A1 dan CYP1B1. Dengan demikian, isokuersitrin berpotensi dalam menghambat patogenesis dan patofisiologi KKR dan dapat diusulkan sebagai terapi adjuvan dengan biaya dan efek samping minimum.

Kata kunci: *kanker kolorektal, pengobatan herbal, kulit manga, terapi ajuvan, Wnt//β-katenin, isokuersitrin*

INTRODUCTION

Colorectal cancer (CRC) is a prevalent malignancy, being the third most common malignancy in men (1,065,960 cases), the second most common in women (865,630 cases), and the second deadliest cancer worldwide in 2020 (935,173 cases).[1,2] In Indonesia, colorectal cancer is the third most prevalent cancer after breast and lung cancer. According to the Global Cancer Incidence, Mortality, and Prevalence (GLOBOCAN) data by the World Health Organization (WHO), CRC incidence in Indonesian men was estimated to be around 21,000 cases and ranked second among all cancers. Meanwhile, among Indonesian women, it became the fourth most prevalent cancer, with around 12,000 cases in 2020.[1,3] Generally, CRC has a significant upward incidence trend among Asian patients, and growing annually by +2.23%, +1.98%, and +2.38% in all ages, old, and young patients from Indonesia. More alarmingly, young patients' colon cancer rates rose noticeably (+9.24%), although rectal cancer trends are generally steady or declining; the persistent pattern of rising CRC and colon cancer incidence was also predicted to have a considerable future impact on the Indonesian population.[4] CRC has a mostly dismal prognosis, depending on its clinical stage. The five-year survival rate for colorectal cancer in Asia has remained at roughly 60% during the past ten years, with the total remission rate remaining unchanged. The countries with the highest survival rates were China and India, respectively.[5] Invasion, progression, or effects of cancer therapy are the three hazards associated with CRC.[6]

Chemotherapy is considered as a standard treatment for CRC and is crucial to enhancing prognosis. It works well in preventing tumor growth, shrinking the tumors, and hampering disease progression.[7] However, current chemotherapy regimens for CRC has certain drawbacks, including inadequate selectivity, insufficient concentrations in tumor areas, systemic toxicity, and increasing prices.[8] Additionally, chemotherapy has several adverse effects, such as diarrhea, post-chemotherapeutic peripheral neuropathy, nausea, and vomiting, limiting its clinical usage and lowering patients' quality of life (QOL), while also gradually increasing chemoresistance.[9–11] Despite advancements in treatment methods to cope with the adverse effects of chemotherapy, these methods still have drawbacks towards the comfort and needs of chemotherapy patients.[12–14] Other therapies, such as surgical resection, can be complicated by massive bleeding and other side effects.[6] Radiotherapy risks patients of having skin toxicity, pelvic fractures and infertility.[15,16] Therefore, alternative therapies must be developed to compensate for these adverse effects. These include adjuvant therapies, which are additional therapies impacting disease progression with minimal side effects compared to other methods of CRC treatment. Plant flavonoids could be one of such emerging therapies, being natural chemicals with various potential biological effects of interest in CRC therapy, including antioxidant, anti-inflammatory, and antitumor effects. One of these flavonoids in particular is isoquercitrin, a main glycoside of the natural flavonol, quercitrin.[16] Biomolecular research on CRC pathogenesis continues to find molecular targets able to be intercepted by flavonoids. In particular, the Wnt/β-catenin signalling pathway plays a significant role in CRC pathogenesis and is seemingly able to be intercepted by isoquercitrin.[17,18] Isoquercitrin also has less cytotoxic effects than its isomer, quercitrin, although both are potential inhibitors of CRC.[19]

Due to their excellent bioavailability, safety, low risk of side effects, and most significantly, cost-effectiveness due to their abundance, plant-derived natural chemicals are currently receiving interest in treating cancer. Flavonoids have grown in relevance

as anticancer drugs and have demonstrated significant promise as cytotoxic anticancer agents that encourage apoptosis in cancer cells. Mangoes (*Mangifera indica*), a well-known fruit tree in Indonesia, primarily producing a byproduct of mango peel, contains abundant flavonoids, including isoquercitrin which has anticancer and anti-inflammatory effects. Therefore, this review aims to outline the latest evidence regarding the use of isoquercitrin extracted from mango peels in inhibiting CRC carcinogenesis, emphasising its effects on the Wnt/β-catenin signalling pathway. Consequently, isoquercitrin is expected to be a clinically viable adjuvant therapy for CRC.

Molecular Basis: The Carcinogenesis of Colorectal Cancer

Colorectal cancer develops through multiple molecular pathways, and understanding its onset and progression, especially its molecular and genetic basis, is essential to discover new targets for pharmacotherapy.[20] In this review, starting from a molecular level, we explored the benefits of the abundant flavonoid isoquercitrin, to be proposed as an adjuvant therapy to CRC. Additionally, its mechanism of action and pharmacological characteristics are also discussed.

There are several molecular bases of CRC in developing tumorigenesis in the bowel and rectum, including pathway of chromosomal instability (CIN), microsatellite instability (MSI), and serrated neoplasia.[21] About 80% of CIN cancer pathways are sporadic and have been shown to have APC mutations, a protein produced by a multifunctional tumor suppressor gene on 5q22.2, leading to the activation of the Wnt signaling pathway, an essential and initiating event in the development of CRC.[22]

A. In the Wingless-related integration site (Wnt) "ON" state, when the Wnt protein is ligated to the low-density lipoprotein receptor-related protein (LRP5/6) and frizzled protein receptors, the cytoplasmic dishevelled protein (DVL) is activated, suppressing glycogen synthase kinase-3α (GSK3). Stabilized β-catenin then moves into the nucleus and interacts with T cell factor (TCF)/lymphoid enhancer factor (LEF) transcription factors to activate the transcription of target genes.
B. In the Wnt "OFF" state, with the absence of

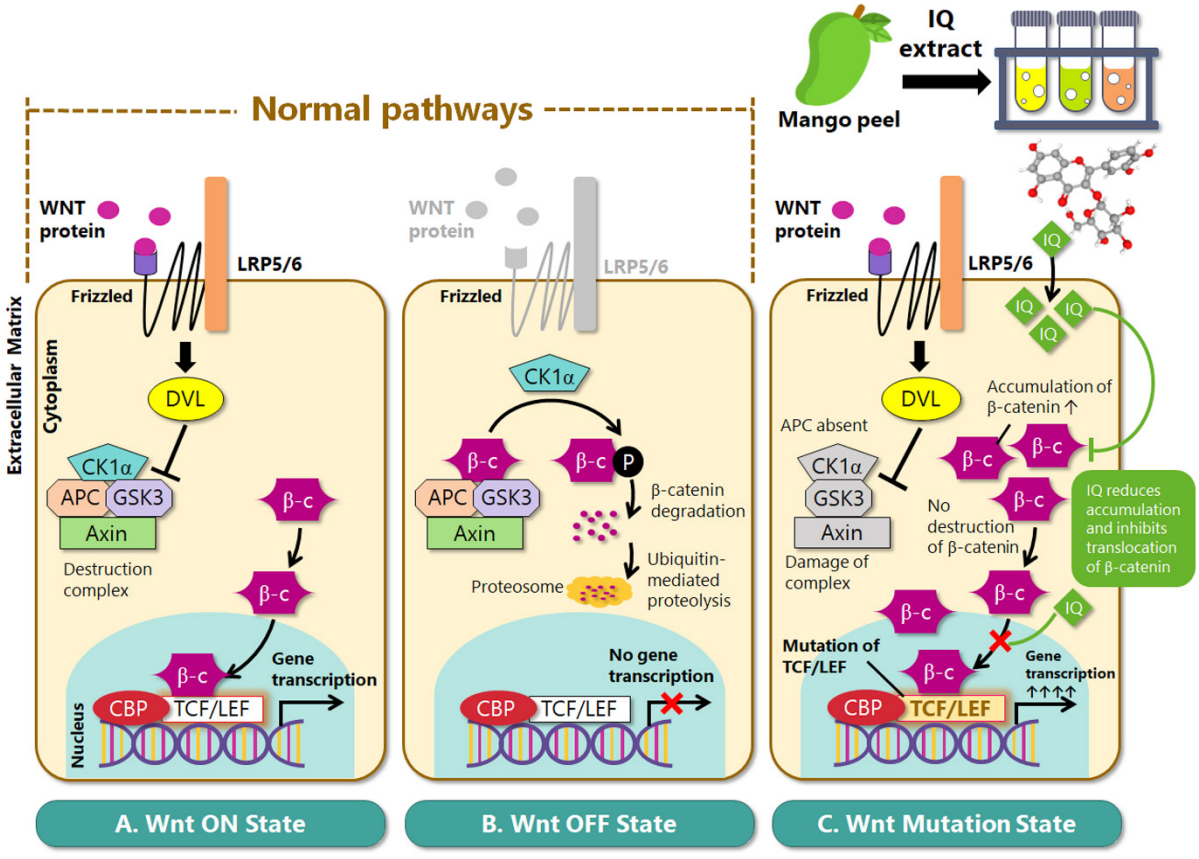

Figure 1. A diagram of the Wnt/β-catenin signaling pathway in both an activated and inhibited state[23–27]

the Wnt ligand, β-catenin is phosphorylated by the β-catenin destruction complex, a tertiary protein complex made up of axin, casein kinase-1 (CK1), GSK3, and adenomatous polyposis coli (APC) protein. Ubiquitin-induced proteasomal degradation then occurs.

C. In the scenario of Wnt mutation, the APC protein is absent, causing cytoplasmic β-catenin accumulation and changes in the TCF/LEF-encoding genes that enhance the nuclear β-catenin accumulation and trigger transcription of genes that promote carcinogenesis of the colorectal crypts. Interestingly, cytoplasmic β-catenin levels can be decreased by mango peel isoquercitrin (IQ), thus inhibiting the translocation of cytoplasmic β-catenin into the nucleus. These steps will generally reduce the transcription of proto-oncogenes and inhibit carcinogenesis.[23–27]

As depicted in Figure 1, the Wingless-related integration site (Wnt)/β-catenin signaling pathway has three possible states. In mammals, there are 19 different types of Wnt, an evolutionarily conserved family of secreted glycoproteins. During canonical Wnt signaling or the Wnt on state, Wnt/β-catenin signalling is modulated by T cell factor (TCF)/lymphoid enhancer factor (LEF), the Wnt ligand, and the secretion of Wnt inhibitors. The binding of Wnt to the Frizzled/low-density lipoprotein-related protein 5/6 (LRP5/6) receptor complex causes the cytoplasmic protein dishevelled protein (DVL) to be activated and suppresses the glycogen synthase kinase-3β (GSK3β) as one of component of the β-catenin destruction complex.[23–27] This destruction complex consists of several proteins, including the adenomatous polyposis coli protein (APC), glycogen synthase kinase-3β (GSK-3β), axin, dan casein kinase-1α (CK1α), functions to destroy accumulated β-catenin in the cytoplasm thus stabilizing its concentration. Once DVL is activated, and the destruction complex is suppressed, stabilized concentrations of β-catenin are translocated to the nucleus, where it interacts with TCF/LEF transcription factors. With its binding proteins, TCF/LEF and β-catenin will modify the expression of a set of target genes that regulate oncogenes, and cell cycle genes, triggering the development of normal cells and controlling embryonic development, proliferation, cellular polarity, and cellular differentiation. The cyclic adenosine monophosphate (cAMP)-response element-binding protein-binding protein (CBP) is one of the many co-activators of β-catenin-dependent transcription. The CBPs are important transcriptional co-activators crucial for a variety of cellular activities, as well as being involved in cancer and pathological states in humans.[23,24]

In the overproduction of β-catenin, also called the Wnt off state, the degradation rate of β-catenin will increase to prevent heightened translocation of β-catenin into the nucleus.[23] The destruction complex will phosphorylate β-catenin, causing proteasomal ubiquitin-mediated proteolysis and preventing translocation, thus preventing further upregulation of target genes.[24] Thus, this system's critical function in the development of the embryonic axis, cell fate determination, preservation of adult tissue homeostasis, and regeneration highlights the significance of this pathway.

In CRC, over 90% of mutations occur in components of the Wnt/β-catenin signalling pathway causing increased β-catenin concentration. The intestinal crypt stem cells are where the mutations, which can be inherited or acquired, are most likely to arise. APC, β-catenin, and TCF/LEF mutations are among the pathway changes that occur most frequently. In the absence of wild-type APC, β-catenin builds up to heightened concentrations, translocates into the nucleus, interacts with TCF/LEF, and binds to DNA, which causes upregulation of genes crucial for stem cell renewal and differentiation. Additionally, activating mutations in β-catenin are present in 5% of CRC cases. Besides being partners of β-catenin, TCF/LEF transcription factors may also play additional roles in CRC, as evidenced by alterations in TCF/LEF-encoding genes in distinct sets of examined tumours.[23] Along with the degradation of the β-catenin destruction complex through the absence of APC, increased concentrations of cytoplasmic β-catenin translocated into the nucleus, and genetic encoding abnormalities occur from the TCF/LEF factors. The carcinogenesis may be induced by engaging with co-activators such as the Pygopus and B-cell lymphoma 9 (Bcl-9) proteins to activate Wnt target genes such as the proto-oncogene *c-myc* cyclin D1 (*CCND1*) and cyclin-dependent kinase inhibitor-1A (*CDKN1A*), leading to the activation of TCF/LEF target genes related to tumor growth.[23,24]

The association between Wnt/β-catenin and CRC raises the possibility of using Wnt inhibitors as CRC treatments. Therefore, we emphasize the influence of synthetically created or naturally extracted small molecules on the modulation of the Wnt/β-catenin signaling pathway.[23] Treatment with the β-catenin

inhibitor isoquercitrin inhibits the growth of tumors in CRC by lowering the abnormal expression of Wnt target proteins associated with carcinogenesis.[25,26]

Isoquercitrin Extracted from Mango Peels: A Natural Remedy for Colorectal Cancer

Consumer interest in mango (*Mangifera indica*) has increased in the last few decades due to its potential to prevent chronic diseases. Mangoes are the fruit with the fourth highest production in the world, after grapes, apples, and bananas. Indonesia is the fourth largest producer of mangoes in the world, and mangoes are one of the 20 highest commodities produced.[28] Many polyphenols are contained in mangoes, showing superior anticancer activities, especially against CRC cell lines.

Before we discussed the findings, we assessed the validity of all main studies that we used within this review. A full assessment of their validity can be read in Table 1 and 2. In general, the studies presented here are valid according to the Office of Health Assessment and Translation (OHAT) risk of bias rating tool (for in-vitro and animal studies) and Oxford Center for Evidence-Based Medicine (CEBM) critical appraisal tools (for studies on humans), with only minor issues of clarity on their blinding and concealment, which is inherent to the experimental study design.[29,30]

The efficacy of extracts of various mangoes (especially Ataulfo and Haden mangoes) in inhibiting CRC cell growth is tested in the CRC SW-480 cell line, which with a phenolic content of 5 mg gallic acid equivalent (GAE)/L, can inhibit the growth of cancer cells up to ~72% without limiting the growth of normal colon cells. This inhibition is linked to the expression of pro-apoptotic biomarkers and cell cycle regulator mRNAs, as well as the reduction of reactive oxygen species (ROS).[31] Polyphenols including quercitrin, kaempferol glycosides, phenolic acid, gallic acid glycosides, and mangiferin are identified in all mango parts.[32] Out of the various polyphenols with various bioavailability, isoquercitrin is the most absorbable in the body.[33] It also has less toxicity than other aglycon flavonoids.[9] Mangoes are well-known agricultural commodities widespread in many tropical developing countries, particularly equatorial ones. They are consumed as dessert, juice, syrups, and other forms of cuisine worldwide, creating a neglected byproduct of mango peel and kernel, around 35–60% of the entire mango.[34] Research estimates that mango peels contain the highest concentration of polyphenols, with the total polyphenol content of mango peels being 4,066 mg/kg of mango peel (Table 3).[34–35] Extraction of isoquercitrin and other flavonoids from peel and kernel waste, therefore, might be a sustainable way of gaining these pharmacologically beneficial compounds.

A study proving the inhibitory properties of isoquercitrin against CRC uses African clawed frog (*Xenopus* spp.) embryos as animal models due

Table 1. Summary of critical review of validity aspect for included in-vitro/in-vivo studies[29]

Studies (Year)	Appraisal criteria								
	Selection bias		Performance bias		Exclusion bias	Detection bias		Selective reporting bias	
	Randomisation	Concealment	Identical experimental condition	Blinding of research personnel	Minimal and rational attrition/ exclusion	Confidence in exposure characterisation	Confidence in outcome assessment	All measured outcomes reported	Other potential threats to internal validity
Makino et al, 2009[45]	●	●	●	●	●	●	●	●	●
Cermak et al, 2003[43]	●	●	●	●	●	●	●	●	●
Amado et al, 2014[25]	●	●	●	●	●	●	●	●	●
Noratto et al, 2010[31]	●	●	●	●	●	●	●	●	●
Chaudhary et al, 2006[46]	●	●	●	●	●	●	●	●	●

Notes: Definitely low risk of bias (●); probably low risk of bias (●); probably high risk of bias/insufficient information (●); definitely high risk of bias (●)

Table 2. Summary of critical review of validity aspect for included clinical trial studies[30]

Studies (Year)	Appraisal criteria				
	Randomisation	The similarity of baseline characteristics	The similarity of treatment outside of the intervention	Loss to follow-up and intention-to-treat analysis	Blinding
Olthof et al, 2000[44]	🟢	🟢	🟢	🔴	🟡

Notes: Yes, clearly stated in the study (🟢); Unclear (🟡); No, definitely not matched with the criteria (🔴)

Table 3. The polyphenol contents of mango peel per kg weight[34,35]

Flavonoid components contained	Amount (mg/kg of raw dried mango peels)	Amount (mg/kg of pure mango peel extract)
Mangiferin	1690.4	1190.9
Mangiferin gallate	321.9	51.9
Isomangiferin	134.5	97.7
Isomangiferin gallate	82.0	19.7
Quercetin 3-O-galactoside	651.2	Not detected
Quercetin 3-O-glucoside (isoquercitrin)	557.7	31.0
Quercetin 3-O-xyloside	207.3	Not detected
Quercetin 3-O-arabinopyranoside	101.5	Not detected
Quercetin 3-O-arabinofuranoside	103.6	Not detected
Quercetin 3-O-rhamnoside	20.1	Not detected
Kaempferol 3-O-glucoside	36.1	Not detected
Rhamnetin 3-O-galactoside/glucoside	94.4	4.3
Quercetin	65.3	23.4
Ellagic acid	Not detected	Traces
Total	4066.0	1418.8

to embryonic molecular pathways such as sonic hedgehog, Wnt, Notch and BMP also playing a role in tumour metastasis.[36] Isoquercitrin is found to affect the Wnt molecular signalling pathway, which causes developmental disorders in *Xenopus* embryos, most notably axial defects, highlighting the role of Wnt as a paracrine molecule affecting embryonic axial development.[37–39] Morphological analyses of the results of this study suggest that the Wnt/β-catenin is affected through the administration of isoquercitrin, resulting in abnormal phenotypes, including eye position decline (33%), microcephaly (23%), and acephaly (18%).[37] Another study uses the Siamois reporter assay (S01234-Lux) to induce Wnt canonic signalling.[37,38] When *xWnt8* mRNA is introduced into the *Xenopus* embryo, there is a ten-fold induction of siamois-luciferase reporter activity, which decreased five-fold with isoquercitrin. Concurrently, isoquercitrin significantly reduced the endogenous expression of *Xnr3*, a target gene of Wnt signalling. Similar tests using RKO-BAR/Renilla cells incubated with Wnt3a-conditioned media (Wnt3a-CM) and given increasing doses of isoquercitrin revealed inhibition of 70% of cellular activity when given 150 µM of isoquercitrin.[37]

Isoquercitrin also affects canonic Wnt signalling by preventing β-catenin translocation to the cell nucleus, as shown in Figure 1c.[38] Additionally, through epistatic analysis using specific activators of various points in the Wnt/β-catenin molecular pathway injected into *Xenopus* embryo, it is proven that the addition of isoquercitrin reduced activation of signals induced by Wnt8, LRP6, β-catenin WT, and β-catenin S33A mRNA as the stable form of β-catenin translocated into the nucleus.[37,39] This did not occur when embryos were injected with Lef1 ΔN VP16 mRNA due to Lef1 responding with cytoplasmic accumulations of β-catenin, causing increased nuclear translocation, and shows that isoquercitrin only inhibits translocation of stable β-catenin.[38,40]

Isoquercitrin also affects the phosphorylation of β-catenin in CRC cells.[37] Phosphorylation of β-catenin, mediated by GSK-3β, allows β-catenin to be degraded by the proteasome through ubiquitinated proteolysis.[40,41] This degradation is a crucial step in preventing the accumulation of β-catenin. Administration of isoquercitrin in several different CRC cell lines, DLD-1, HCT116, and SW480, increased phosphorylation of β-catenin and caused decreasing concentrations of β-catenin in the HCT116 and SW480 cell lines.[37]

In HCT116, isoquercitrin increased phosphorylation of β-catenin with enough significance that this cell line is used to study further the localization of β-catenin and levels of *CCND1* (the Wnt target gene in HCT116). Isoquercetrin affects β-catenin localization by inducing massive accumulations of β-catenin in the cytoplasm and reducing nuclear concentrations

of the molecule.[37] As a result, cyclin D1 levels in the HCT116 cells under this investigation were also reduced.[42] To assess the toxicity of isoquercitrin and its effects on the morphology and viability of each cell line, immunocytochemistry and MTT tests were used. It revealed that isoquercitrin did not affect cellular morphology in all CRC cell lines analyzed.[37] Another study comparing isoquercitrin and quercitrin on the HCT116 cell line, also showed that quercitrin massively reduced cellular viability 12 hours after administration and drastically decreased the number of cells in 24 hours, while isoquercitrin only affected cellular viability after 48 hours.[37,45] However, this does show that both flavonoids are not cytotoxic.[37]

A crucial effect of isoquercitrin is its inhibition of the proliferation of various CRC cell lines. Isoquercitrin inhibits the proliferation of CRC cells without affecting the growth of non-cancer cells. Proliferation assays of SW480, HCT-116 and DLD-1 cell lines in DMSO demonstrated a cellular proliferation ratio of 40%, 39%, and 42%, respectively, which decreased to 24%, 18%, and 17%, respectively, with isoquercitrin administration. The proliferation of non-cancer control cells was not affected. Isoquercitrin can also inhibit CRC cell line migration, which was studied using a migration assay. In the first 18 hours of the trial, cell lines (DLD-1, HCT116, SW480, and non-cancer cells) in DMSO exhibit a migration ratio of 14%, 13%, 22%, and 25%, respectively. When treated with isoquercitrin, migration of cancer cell lines significantly decreased to 7%, 8%, and 8%, respectively, without affecting the migration of non-cancer cells.[37]

The Applicability of Isoquercitrin as an Adjuvant Therapy for Colorectal Cancer

For bedside use, isoquercitrin is most ideally administered orally, due to its higher oral bioavailability than other similar flavonoids.[9,16] A single oral dose of 148 mol/kg of isoquercitrin in a porcine model has a relative bioavailability 121% higher than rutin (quercetin-3-O-glucorhamnoside) and 48% higher than quercitrin.[43] In humans, isoquercitrin reached maximum plasma concentration in 37 ± 12 minutes and is excreted in 1,110 ± 48 minutes.[44] The substance is more water-soluble than other flavonoids, with a solubility of 206 µmol/L.[45]

Isoquercitrin is extensively metabolized in the guts and the liver. A daily intake of 5.4 mg/kgBW of isoquercitrin has been found to have an effective anticancer effect. However, in high doses, this substance can cause chromaturia.[16] Several drug interactions may also occur due to the inhibitory effect of this substance on several CYP450 metabolizing enzymes, including CYP1A1 and CYP1B1 in humans.[46] However, at this point, no thorough toxicology study has been done to evaluate the toxicity of isoquercitrin. Nevertheless, a similar molecule, quercitrin, was evaluated for its toxicity in 2010, with conclusions that it is generally considered safe.[47] Most possibly, isoquercitrin, a similar molecule, would also be a safe and prospective inhibitor of CRC activity.

Regarding clinical applicability, as reflected in Table 4, research on isoquercitrin is admittedly still preliminary, and applicability issues must be addressed in future research. Most studies cited are preclinical; therefore, causality cannot always be concluded. There is, therefore, a need for high-level evidence, such as randomized controlled trials (RCTs), meta-analyses, systematic reviews, and cohort studies. Phase I–III

Table 4. Summary of critical review of applicability aspect for all included studies[30]

Studies (Year)	Appraisal criteria			
	Applicability of results to the patient	The similarity of patient's characteristic	Findings are essential and beneficial	Clinical practice consideration of proposed treatment
Olthof et al, 2000[44]	🟢	🟢	🟢	🟡
Makino et al, 2009[45]	🟡	🔴	🟢	🟡
Cermak et al, 2003[43]	🟡	🔴	🟢	🟡
Noratto et al, 2010[31]	🟡	🟡	🟢	🟢
Amado et al, 2014[25]	🟡	🔴	🟢	🟡
Chaudhary et al, 2006[46]	🟡	🟡	🟢	🟡

Notes: Yes, clearly stated in the study (🟢) ; Unclear (🟡); No, definitely not matched with the criteria (🔴)

pharmacological studies will also be vital to assess the substance's efficacy and clinical safety. These studies will therefore help figure out the bedside applicability of this phytochemical.

CONCLUSION

Current treatment of colorectal cancer would benefit from efficacious adjuvant therapies with low cost and minimal side effects. The evidence reviewed in this article confirmed that several CRC cell lines (HCT-116, DLD-1, and SW480), unifed by mutations in the Wnt/β-catenin molecular pathway, can be inhibited through isoquercitrin administration. Oral isoquercitrin has the maximum amount of bioavailability and minimum toxicity and is highly water-soluble, making it pharmacologically superior to other anticancer flavonoids. The substance is also available in mango peel, a hitherto unused byproduct of the fruit industry. To sum up, isoquercitrin is a potential adjuvant therapy in inhibiting CRC growth through inhibition of the Wnt/β-catenin pathway, and has minimum costs and side effects. Randomised controlled trials are required to investigate the effects of the substance in indicated patients. Other stakeholders, such as the government and the pharmaceutical industry, should develop research on the efficient extraction of isoquercitrin for maximum use as a potential anticancer agent in CRC.

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