Review

Leptin and Adiponectin as Immunohistochemical Biomarkers in Colorectal Cancer: Publication Trends and Research Advances

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Featured Application

Leptin and adiponectin immunohistochemical expression patterns in colorectal malignancy can be used for better patient stratification. Data about the role of these two adipokines in colorectal tumorigenesis highlights their potential in improving diagnostic accuracy. Additionally, the analysis of research trends identifies key gaps in biomarker-driven studies in colorectal cancer.

Abstract

Background: Leptin and adiponectin play a key role in obesity-associated malignancy, particularly in colorectal cancer (CRC). Immunohistochemical (IHC) evaluation of these adipokines may offer valuable prognostic insights in CRC. This study aimed to analyze global publication trends and summarize current knowledge on the potential of these hormones as IHC biomarkers in CRC. **Methods:** A problem-oriented bibliometric analysis, including publications from 2000 to 2025 was performed across MEDLINE and Scopus databases. In parallel, a literature review was conducted to present the biological and clinical relevance of these adipokines in CRC. **Results and Discussion:** A total of 101 publications were identified. Scopus indexed substantially more studies than MEDLINE. The journals *Cancer Research, Journal of BUON, Cells, BMC Cancer*, and *Asian Pacific Journal of Cancer Prevention* were identified as the core journals publishing on this topic over the 25-year period. Leading countries were China and USA. A review of the literature showed that adiponectin is a promising prognostic marker, while leptin appears to be a better indicator of disease progression. **Conclusions:** IHC research on leptin and adiponectin in CRC is a promising but still underexplored area. Their integration with routine molecular assessment has the potential to improve patient stratification.

Keywords: immunohistochemical biomarkers; colorectal cancer; leptin; adiponectin; publication trends

1. Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy globally [1,2] and the second leading cause of cancer-related deaths worldwide in 2022 [2]. The global burden of CRC is projected to increase by 60% by 2030 [3]. Moreover, results from the Global Burden of Disease

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Study, 2021 demonstrate that during the period from 1990 to 2021, there is an increase of 130.97% in disability-adjusted life years and of 130.24% in deaths associated with early-onset colorectal cancer as well as 133.32% and of 139.71% associated with late-onset colorectal cancer, respectively [4].

Data from the Global Cancer Observatory (GLOBOCAN) database demonstrates that in 2022, there are 1 926 425 global CRC incident cases and 904 019 deaths [5]. If CRC incidence rates remain unchanged, the global new cases are projected to increase by 22.51% and to reach 2.36 million by 2050. This alarming trend underlines the emergent needs of identifying new biomarkers for reliable and precise diagnosis of this highly heterogeneous malignancy. Adipokines, particularly leptin and adiponectin, are well known master modulators of colon carcinogenesis [6], especially tumorigenesis that is closely linked to obesity [7]. Leptin possesses robust proliferative, pro-inflammatory and proangiogenic activities promoting tumorigenesis [8], while adiponectin usually exerts strong anti-tumorigenic characteristics [9]. In addition, the leptin/adiponectin ratio is a promising indicator for the colorectal pathogenesis and progression [2]. All these findings suggest that dysregulation in the expression of these two adipokines in colorectal tissue samples could be a promising and reliable biomarker for CRC.

Currently, TNM classification is the basis for predicting patient prognosis in CRC [10]. For better patients' stratification, a decade ago a transcriptome-based system was invented, the consensus molecular subtype (CMS) classification. It classifies colorectal tumors into four subtypes with different molecular and genetic characteristics: CMS1 (immune), CMS2 (canonical), CMS3 (metabolic), and CMS4 (mesenchymal) [11]. CMS2 subtype defines the best overall survival among the patients while CMS4 subtype determines the worst prognosis. This classification is the most popular transcriptome- based system [12], but it is too expensive for routine clinical applications. That is why alternative and clinically useful immunohistochemical (IHC) methods are needed. One such IHC classifier using five biomarkers, FRMD6, ZEB1, HTR2B, and CDX2, was proposed by Trinh et al. [13]. The main limitation of this classifier was that it was unable to distinguish CMS2 tumors from CMS3 tumors. Thus, in 2021, Lee and his colleagues proposed the inclusion of β-catenin staining in this IHC panel which allowed the differentiation of these two subtypes [14]. All these findings demonstrate the potential clinical utility of IHC-based biomarkers for better patient stratification.

Despite these advances in molecular classification, the clinical implementation of transcriptome-based subtyping remains restricted by cost and technical complexity, underscoring the continuing demand for accessible IHC-based prognostic tools applicable to formalin-fixed, paraffin-embedded (FFPE) tissue. In this context, adipokines, leptin and adiponectin in particular, have attracted growing interest as candidate IHC biomarkers, given their mechanistic involvement in obesity-driven colorectal carcinogenesis and the feasibility of their detection using standard IHC protocols. To date, however, no comprehensive synthesis of the available evidence on the clinicopathological correlates and prognostic significance of leptin and adiponectin IHC expression in CRC has been published. An illustrative example of such approach can be found in the emerging field of adipobiology.The results from a retrospective problem-oriented search in *MEDLINE* and *EMBASE* databases available via OVID between 1980 and 2007 using several essential terms as key words such adipose tissue, adipokine(s), adipocytokine(s), adiponectin, and leptin reveal that 11 papers only under the term of 'adipobiology' have been abstracted during this period [15]. Some aspects of the dynamic growth of the world publication output in basic, transitional and clinical adipobiology as compared with some other recently emerging topics are demonstrated and certain elements of adipology future development from a bibliometric point of view are traced.

Another example illustrating the application of bibliometric methodology is provided by studies on breast cancer immunohistochemistry. The bibliometric analysis of the publications abstracted inWoS, MEDLINE and BIOSIS as well as in Scopus during the period between 2003 and 2018 within a retrospective problem-oriented based search reveals several essential patterns of the dynamic science institutionalization on breast cancer IHC [16]. There are 1187 publications in 288 journals abstracted in WoS, 776 publications in 140 journals abstracted in BIOSIS, 711 publications in 156 journals abstracted in Scopus, and 616 publications in 234 journals abstracted in MEDLINE. The

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complex bibliometric methodology presenting with the capacities of the constellation of bibliometric indicators can be purposefully used for integrated assessment of science institutionalization under the conditions of internationalization and for timely identification of the essential patterns of scientific advances in hot topics.

In addition, a retrospective, problem-oriented search was performed in June 2017 to assess the institutionalization of research on colorectal tumour markers [17]. The search covered the period 1987–2016 and included the WoS, Scopus, MEDLINE, and BIOSIS databases. A total of 497 publications were identified in Web of Science, 427 in Scopus, 370 in BIOSIS, and 368 in MEDLINE. The retrieved articles were published in multiple languages across 136–197 journals. Furthermore, they were authored by researchers from 37–50 countries, depending on the database. All these findings provide a broad overview of the global research activity in this field and may be of particular interest to coloproctologists, science policy managers, and journal editors, especially in smaller countries seeking greater international visibility.

The objective of the present study was to present some essential results from the publication trends devoted to the application of IHC for the assessment of leptin and adiponectin as prognostic biomarkers in CRC. Our goal was to synthesize current data on adipokines as potential prognostic markers in CRC applicable through IHC, using an integrated approach involving descriptive bibliographic analysis and literature review.

2. Materials and Methods

2.1. Databases

The bibliometric analysis data in the current research was retrieved from MEDLINE and Scopus databases. These databases were selected because of their extensive coverage of peer-reviewed literature related to IHC studies in oncology, which ensures a comprehensive data set for evaluating the diagnostic and prognostic implications of cancer-related biomarkers.

2.2. Search Strategy, Inclusion and Exclusion Criteria

In October 2025, a retrospective search focused on the subject was performed among articles published between 2000 and 2025, using the MEDLINE and Scopus databases. The publications dealing with these two adipokines, leptin and adiponectin as IHC prognostic biomarkers in CRC patients were included in the analysis. Both databases were searched independently using the following Boolean search string: (“immunohistochemistry OR “immunohistochemical biomarkers” OR “IHC markers”) AND (“colorectal cancer” OR “colorectal malignancy” OR “colorectal carcinoma” OR “CRC”) AND (“leptin” OR “adiponectin” OR “adipokines” OR “adipocytokines|). The search was applied across title, abstract, and keyword fields, with no additional database-specific field restrictions. Results were limited to English-language publications and to original research articles, excluding reviews, editorials, letters, conference abstracts, book chapters, and non-full-text records. The inclusion criteria required: peer-reviewed original research articles reporting IHC assessment of leptin and/or adiponectin in human CRC tissue samples. The exclusion criteria comprised: animal or in vitro studies; studies reporting serum or plasma biomarker levels without tissue IHC data; review articles and meta-analyses; conference abstracts and non-peer-reviewed records; and duplicate entries identified across databases.

The low number of identified publications (n = 101) reflects the focused scope of the search strategy. It was deliberately designed to include studies reporting IHC assessment of leptin and adiponectin specifically in colorectal cancer tissues. This specificity results in a smaller pool compared to broader searches for adipokines.

Citations per article were also retrieved from each database. The following bibliometric parameters were comparatively assessed across both databases: (i) annual and cumulative publication output; (ii) distribution of publications across journal titles; and (iii) geographic

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distribution of contributing authors by country of affiliation. Citation counts per article were additionally retrieved where available.

2.3. Literature Search

Scopus and Medline datasets were searched between September and December 2025 for English full-text articles (2000–2025) on the correlation between IHC expression of leptin and adiponectin and colorectal cancer in patients. Key words include "colorectal cancer," "adipokines," "adipocykines," "immunohistochemistry," "adiponectin," "leptin," "obesity," and "biomarkers". This research was focused on the association of protein expression and clinicopathological parameters.

3. Results

3.1. Annual Publication Output

The distribution of publications during the investigation period shows a growing interest in IHC studies of leptin and adiponectin in CRC. 45 publications on leptin were retrieved in Scopus and 20 in MEDLINE. In Scopus, the largest number of articles were published in 2021–2025 (40.0%, n=18), while the entries in MEDLINE are most prevalent in 2011–2015 (45.0%, n=9) (Table 1).

Table 1. Annual dynamics of the number and relative share of the publications on leptin abstracted in Scopus and in MEDLINE.

Year span	Scopus		MEDLINE	
	n	%	n	%
2000- 2010	11	24,44	5	25,00
2011-2015	9	20,00	9	45,00
2016-2020	7	15,56	3	15,00
2021-2025	18	40,00	3	15,00
total	45	100,00	20	100,00

For adiponectin, 28 publications were indexed in Scopus and 8 in MEDLINE, with the largest percentage again in 2021–2025 (39.28%, n=11) in Scopus, while publications in MEDLINE reached their peak in 2011–2015 (62.5%, n=5) (Table 2). In general, the results indicate a relatively recent increase in scientific publications, particularly in the literature indexed in Scopus.

Table 2. Annual dynamics of the publications on adiponectin abstracted in Scopus and in MEDLINE.

Year span	Scopus		MEDLINE	
	n	%	n	%
2000-2010	5	17,86	0	0
2011-2015	7	25,00	5	62,50
2016-2020	5	17,86	2	25,00
2021-2025	11	39,28	1	12,50
total	28	100,00	8	100,00

The publication output demonstrated a generally increasing trend, indicating a growing scientific interest in adipokine-related biomarkers in colorectal cancer research. An initial phase characterized by several sporadic publications is observed during the early years (2000-2010). After 2021 the publication activity related to IHC studies of leptin and adiponectin in CRC increased significantly. This finding aligns with the expanding interest in the role of obesity in malignant transformation. The most productive period was 2021-2025. It is characterized by 33 publications associated with the current topic, accounting for 32.67% of the total output. The highest publication activity is observed in the nearest period (2021–2025). This trend is particularly notable for studies related to leptin in Scopus. Publications related to adiponectin show a similar but less prominent

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trend. In contrast, MEDLINE indexes fewer studies, with most publications concentrated between 2001 and 2015. The combined annual dynamics of publications in Scopus and MEDLINE are illustrated in Figure 1.

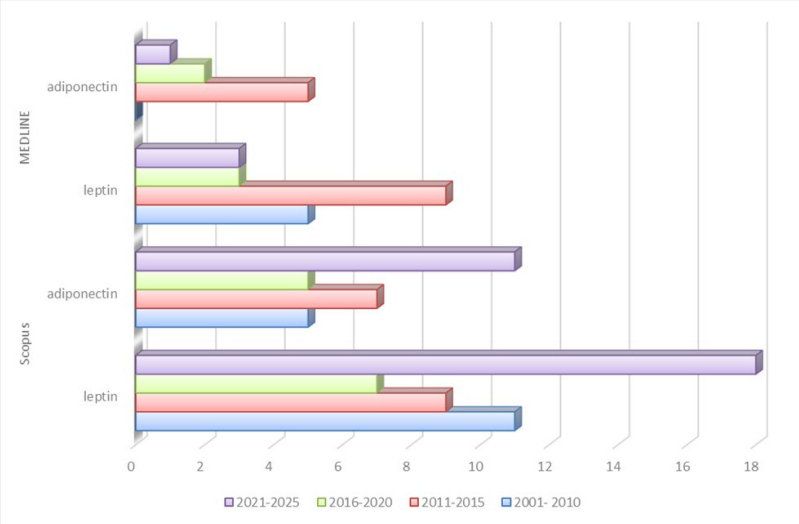

Figure 1. Combined annual dynamics of publications in Scopus and MEDLINE focused on leptin and adiponectin.

The number and relative proportion of publications on leptin and adiponectin abstracted in Scopus were 2.25-fold and 3.5-fold higher, respectively, than those indexed in MEDLINE. These findings highlight substantial differences in database coverage.

3.2. "Core" Journals Publishing on Leptin in Colorectal Malignancy

A total of 45 publications indexed in Scopus and 20 publications indexed in MEDLINE were identified for leptin-related IHC studies in CRC. The distribution of articles across journals demonstrated a marked dispersion pattern. In the Scopus dataset, three journals, *Cancer Research*, *Journal of BUON*, and *Cells* represent 4.44% of the total output per journal (Table 3). Collectively, these three journals accounted for 6 of 45 publications (13.33%). In MEDLINE, two journals, *Cancer Research* and *Journal of BUON* correspond to 10.00% of the indexed corpus per journal and 20.00% cumulatively. The journal *Cells* did not appear among MEDLINE-indexed records.No journal published more than two articles in either database, indicating the absence of a dominant publication outlet. There is an overlap of *Cancer Research* and *Journal of BUON* between Scopus and MEDLINE datasets.

Table 3. "Core" journals on leptin abstracted in Scopus and in MEDLINE.

Journal title	Scopus		MEDLINE	
	n	%	n	%
Cancer Research	2	4,44	2	10,00
Journal of BUON	2	4,44	2	10,00
Cells	2	4,44	-	-

3.3. "Core" Journals Publishing on Adiponectin in Colorectal Malignancy

For adiponectin, 28 publications were identified in Scopus and 8 in MEDLINE. The distribution across journals was more dispersed than for leptin (Table 4). In Scopus, *BMC Cancer* was the only journal contributing two publications (7.14%). In MEDLINE, Asian Pacific Journal of Cancer

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Prevention accounted for two publications, representing 25.00% of the indexed literature. No journal overlap was observed between databases for adiponectin-related studies.The higher proportional share observed in MEDLINE reflects the smaller corpus size rather than a stronger concentration effect.

Table 4. "Core" journals on adiponectin abstracted in Scopus and in MEDLINE.

Journal title	Scopus		MEDLINE	
	n	%	n	%
BMC Cancer	2	7,14	-	-
Asian Pacific Journal of Cancer Prevention	-	-	2	25,00

Comparison between Scopus and MEDLINE reveals differences in the centrality patterns of journals. Publications related to leptin show partial agreement between the databases, while studies related to adiponectin show a complete difference in the identified core journals. In addition, all identified core journals are oncology related. The leading journals represent translational cancer research (*Cancer Research*), clinical oncology (*Journal of BUON*), molecular and cellular biology (*Cells*), and cancer focused investigations (*BMC Cancer and Asian Pacific Journal of Cancer Prevention*)

3.4. Geographic Distribution of Leptin and Adiponectin Related Publications

The geographic distribution of authors contributing to leptin-related immunohistochemical studies in CRC is presented in Table 5.

Table 5. Leading countries of authors of papers on leptin abstracted in Scopus and in MEDLINE.

Country	Scopus		MEDLINE		
	n	%	Country	n	%
China	10	22,22	China	3	15,00
USA	7	15,56	South Korea	3	15,00
Japan	5	11,11	Montenegro	2	10,00
UK	4	8,89			
France	3	6,67			
Italy	3	6,67			
South Korea	3	6,67			

In Scopus dataset, China ranked first with 10 publications (22.22%), followed by USA with 7 publications (15.56%), and Japan with 5 publications (11.11%). The UK contributed 4 publications (8.89%), while Italy and South Korea each accounted for 3 publications (6.67%). Together, the top three countries (China, USA, Japan) generated 48.89% of the total Scopus indexed output, indicating moderate geographic concentration. In MEDLINE, China and South Korea shared first position with 3 publications each (15.00%), followed by France (6.67%) and Montenegro (10.00%). These findings are illustrated in Figure 2.

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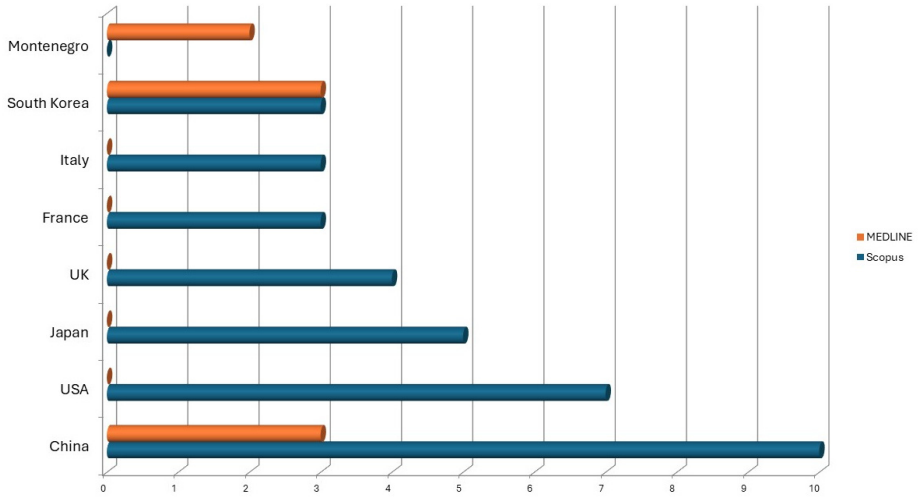

Figure 2. Leading Countries in Leptin Publications Indexed in Scopus and MEDLINE.

The distribution of countries contributing to adiponectin-related studies (Table 6) reveals similar but slightly more regionally concentrated patterns.

Table 6. Leading countries of authors of papers on adiponectin abstracted in Scopus and in MEDLINE.

Country	Scopus		MEDLINE		
	n	%	Country	n	%
China	7	25,00	South Korea	2	25,00
USA	5	17,86	Turkey	2	25,00
Japan	4	14,29			
Greece	4	14,29			
Italy	3	10,71			

In Scopus, China again ranked first with 7 publications (25.00%), followed by the USA with 5 publications (17.86%) and Japan with 4 publications (14.29%). Italy contributed 3 publications (10.71%). Collectively, the top three countries accounted for 57.15% of total Scopus indexed output, indicating stronger concentration compared to leptin-related studies. In MEDLINE, South Korea and Turkey each contributed 2 publications (25.00%), while Greece accounted for 14.29%. This data is illustrated in Figure 3.

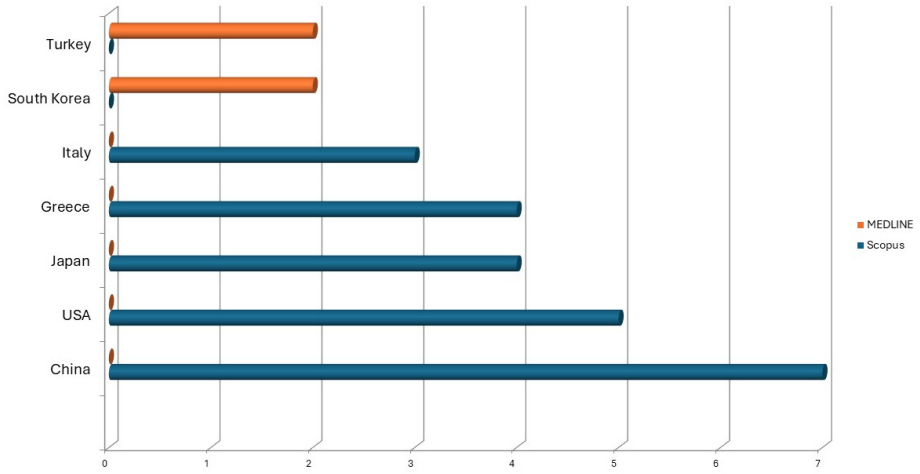

Figure 3. Leading Countries in Adiponectin Publications Indexed in Scopus and MEDLINE.

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Notably, adiponectin-related research demonstrates a pronounced contribution from East Asia and parts of Southern Europe. Unlike leptin research, Western European countries and the United Kingdom are less prominently represented in this subset.

3.5. Literature Review on IHC Biomarkers in CRC with Focus on Leptin and Adiponectin

CRC is a heterogeneous disease that is strongly affected by metabolic and genetic factors. Genetic factors have been well explored over the years. To emphasize the association between metabolic dysregulation and its role in initiation, progression, and prognosis in CRC, we summarized current knowledge into next subsections.

3.5.1. Mechanistic Role of Leptin in CRC

Recent work links obesity-related hyperleptinemia to several cancer "hallmarks" in colorectal cancer (CRC), but data also show context-dependent effects. Numerous studies have reported that leptin and its receptor (LEPR/ObR) are frequently overexpressed in CRC tissue and adenomas, driving mitogenic and anti-apoptotic effects via PI3K/AKT/mTOR, JAK2/STAT3 and MAPK/ERK pathways [18–21]. In addition, increased ObR and STAT3 activation appear in adenomas and are more pronounced in cancers, supporting a role in early and late carcinogenesis [22]. Leptin promotes proliferation, survival, and anchorage-independent growth of colorectal tumor stem cells, implying support of a cancer stem cell compartment. Moreover, recent study indicates that Wnt signaling upregulates ObR. This leads to active leptin–ObR communication that supports tumor growth via STAT3 without altering β-catenin localization [23]. Such activation usually is detected mainly after tumor initiation.

Furthermore, leptin enhances VEGF/VEGFR2 expression and angiogenesis through PI3K, JAK2/STAT3 and ERK1/2, and induces cytokines (CXCL1, CCL2, TGF-β), COX-2, and lipid droplet formation in intestinal epithelial cells via mTOR, linking obesity-driven inflammation to CRC promotion [21]. In addition, obesity-related insulin resistance, hyperinsulinemia, oxidative stress, and altered leptin/adiponectin balance converge on JAK/STAT and PI3K/AKT/mTOR, remodeling CRC signaling [24].

3.5.2. Mechanistic Role of Adiponectin in CRC

In colorectal carcinoma, adiponectin reduces proliferation, adhesion, and invasion, largely via AMPK activation, with downstream effects on mTOR and ERK1/2 signaling and caspase-3–mediated apoptosis [25]. Similar AMPK/mTOR-mediated anti-proliferative effects are emphasized as central to its antineoplastic role in CRC [26]. In addition, adiponectin alters cancer metabolism by downregulating glycolysis-related genes, and by reshaping lipid metabolism, limiting energy supply for tumor growth [25]. Moreover, recent data indicates that low adiponectin promotes insulin resistance and increased IGF-1, favoring proliferation and VEGF upregulation. At the same time, optimal levels of adiponectin inhibit the PI3K/AKT signaling pathway, thereby reducing carcinogenesis, adhesion, and migration [27]. Adiponectin also generally suppresses NF-κB–driven pro-inflammatory cytokines and VEGF, contributing to anti-angiogenic and anti-tumor actions [28].

Data from epidemiologic studies have shown that higher levels of circulating adiponectin are generally associated with lower CRC risk, strengthening its protective profile [24]. In is important to mention that current data also show context-dependent and even opposing effects of this adipokine in CRC. Supporting this, recent research reported that adiponectin may reprogram tumor-associated macrophages toward an M2-like phenotype and increase IL-8 expression, promoting angiogenesis, tumor growth, and recurrence in CRC [29]. In addition, it was reported that in specific colon cancer cell contexts, adiponectin can stimulate growth and inflammatory cytokine secretion via cAMP/PKA, and its effects may vary depending on glucose availability [26]. These opposing effects underpin the bifurcated role of adiponectin in CRC, influenced by tumor stage, microenvironmental cytokines, and metabolic status.

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3.5.3. Immunohistochemical Expression Patterns of Leptin and Adiponectin in CRC

Current studies have demonstrated that altered tissue expression by IHC methods are being explored as diagnostic and prognostic markers in CRC. IHC and molecular studies show that several adipokines, especially leptin, its receptors, and adiponectin and its receptors, are differentially expressed between normal mucosa, adenomas, and CRC. Moreover, the specific expression patterns of these two adipokines show significant correlation with tumor grade, stage and overall survival of the patients. Data reported in the last 10 years was summarized in Table 7 and Table 8.

Table 7. Summary of IHC studies evaluating leptin in CRC patients.

Reference	N (Patients)	Method/Scoring (IHC)	Main Findings
Koda et al., 2007 [30]	166	IHC for leptin; expression was scored as 0 (<10% positive cells), 1+ (10–50%), or 2+ (>50%)	Leptin overexpressed in CRC is associated with poorer differentiation and metastasis
Paik et al., 2009 [31]	437	IHC; expression graded neg/weak/moderate/strong	High leptin expression is associated with better survival of colorectal cancer patients.
Jeong et al., 2015 [32]	146	IHC; expression graded neg/weak/moderate/strong and grouped for analysis	Strong leptin expression observed in subset; inversely associated with nodal stage in this cohort
Al-Maghrabi et al., 2018 [33]	155	Tissue microarray; IHC positive/negative; intensity stratified	Leptin positive in most tumors (≈93.5%); higher expression associated with several adverse features (distant metastasis, recurrence) in subgroup analyses
Li et al., 2020 [34]	407	IHC; high vs low leptin expression; survival analyses, supported by TCGA data	Leptin overexpression correlated with metastasis stage and lymph node involvement
Al-Shibli et al., 2019 [35]	44	IHC; intensity scoring for leptin and LEPR	Tumors showed high intensity of LEP and LEPR versus adjacent normal mucosa
Mahmoudi-Nesheli et al., 2023 [36]	90	IHC for leptin and LEPR; ELISA for serum leptin	Reported tissue expression patterns for leptin and LEPR; no significant difference in leptin and LEPR expression between CRC patients and healthy controls.
Chludzińska-Kasperuk et al., 2023 [37]	61	IHC for leptin and leptin receptor (LEPR) in tissue; ELISA for serum leptin	Higher expression of leptin and LEPR are linked to obesity, suggesting they may influence obesity-associated cancer progression
Parmesh et al., 2024 [38]	60	IHC for leptin and adiponectin receptor; expression was scored as 0 (no positive cells), 1 (<10% positive cells), 2	Leptin positivity significantly correlated with larger tumor size, lymph node and distant

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		(10–50%), 3 (>51-80%) or 4(>80% positive cells)	metastasis, distant metastasis and advanced TNM stage
Hanafy et al., 2024 [39]	60	IHC for leptin and cyclin D1; scoring by intensity	Significantly increased leptin and cyclin D1 expression in CRC; elevated leptin and cyclin D1 are associated with advanced stage, lymph node and distant metastasis.

Table 8. Summary of IHC studies evaluating adiponectin in CRC patients.

Reference	N (Patients)	Method/Scoring (IHC)	Main Findings
Williams et al.,2008 [40]	40	Semiquantitative IHC intensity/percentage, categorized as negative, positive, strongly positive for AdipoR1/R2	Marked increase of both receptors in carcinomas vs normal, suggesting CRC-specific up-regulation
Barresi et al., 2009 [41]	45	IHC using adiponectin antibody	Decreased adiponectin expression in tumor tissue compared to adjacent normal mucosa
Byeon et al., 2010 [42]	100	IHC graded by staining intensity/extent; cases grouped by grade of AdipoR1/R2 immunostaining	Expression of both receptors is inversely related to T stage; lowest expression in poorly differentiated adenocarcinoma;
Nakajima et al., 2010 [43]	119	IHC in CRC tissues; intensity & % scoring	Low adiponectin expression correlated with advanced TNM stage and poor differentiation
Gialamas et al., 2011 [44]	104	IHC staining	Low adiponectin expression correlated with lymph node metastasis
An et al., 2012 [45]	92	IHC staining in paraffin-embedded CRC tissue; H-score	Reduced adiponectin expression in tumor tissue compared to adjacent normal mucosa
Canhoroz et al., 2014 [46]	53	IHC; scoring system for staining intensity	Adiponectin expression is reduced in CRC
Vetvik et al., 2014 [47]	60	IHC for globular adiponectin (gAd) and ADIPOR1; relative staining compared between tumor and mucosa	Adiponectin (mRNA and globular protein) and AdipoR1, were significantly higher in tumors vs adjacent mucosa
Wei et al., 2015 [48]	156	IHC; semi-quantitative scoring (intensity and extent)	Adiponectin expression decreased in high-grade and advanced stage tumors
Zhou et al., 2017 [49]	281	IHC for AdipoR2; cases classified as positive vs negative expression	AdipoR2 protein positivity associated with degree of differentiation, tumor infiltration and lymphatic metastasis
Parmesh et al., 2024 [38]	60	IHC for adiponectin receptors AdipoR1,R2; semi-quantitative scoring; cases grouped as positive vs negative	Negative adiponectin receptor expression significantly associated with advanced tumor stage, lymph node and distant metastasis; combined pattern of positive leptin and negative adiponectin receptor predicted higher metastatic risk

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Data presented in the tables show that multiple IHC studies from recent years have reported that both LEP and LEPR were present at high intensity in cancerous tissues while normal adjacent mucosa demonstrated weak staining [33,35]. Regarding adiponectin and its receptors (AdipoR1, AdipoR2 and T-cadherin) expression patterns in most of the studies are documented significantly reduced levels in CRC tissues compared to the normal colon tissue [44,46]. Furthermore, in 2024 Parmesh and colleagues reported that positive leptin receptor expression and negative ADIPORs have shown strong correlation with larger tumor size, lymph node metastasis, and advanced stage. So, they proposed positive leptin combined with negative adiponectin receptor staining as a marker of metastatic risk [38].

In summary, IHC studies in CRC consistently show frequent and stronger leptin/leptin receptor expression in tumor tissue compared with normal mucosa, often associated with larger, more advanced, and node-positive tumors. In contrast, loss or low adiponectin receptor expression is linked to nodal and distant metastasis and higher stage and grade, supporting an adverse pattern of leptin up-regulation and adiponectin pathway down-regulation in more aggressive colorectal cancers.

All these findings indicate that leptin acts primarily as a factor in progression and metastasis, while adiponectin demonstrates a protective role in tumorigenesis. In summary, adiponectin and its receptors, AdipoRs expression patterns particularly support their use as prognostic and possibly therapeutic targets, while leptin and its receptors, LEPRs, are more promising as progression markers.

3.5.4. Comparison with Other IHC Biomarkers in CRC

The clinical utility of adipokine-based biomarkers should be considered in the context of established IHC and molecular classification systems. Current CRC diagnostics rely on markers such as Ki-67, p53, β-catenin, VEGF and CDX2, as well as transcriptomic classifications such as the consensus molecular subtypes (CMS).

Recent advances in the field of clinically relevant IHC biomarkers in CRC are summarized in Table 9.

Table 9. Key IHC markers in CRC and their clinical significance.

Marker	Biological Role	Diagnostic Utility	Prognostic Value	Clinical Implications	References
CK20/CK7	Cytokeratins	CK20+/CK7− supports colorectal origin	Limited	Differentiates CRC from other primary tumors	[50] [51]
CDX2	Transcription factor	Sensitive/specific for colorectal origin	Loss leads to worse prognosis	Supports diagnosis	[50] [51] [52] [53]
MMR (MLH1, MSH2, MSH6, PMS2)	DNA repair	Loss → MSI/dMMR	Favorable early stage	Guides Lynch + immunotherapy	[54] [55]
BRAF V600E	MAPK mutation	Detects mutant CRC	Poor prognosis	Targeted therapy relevance	[56]
HER2	Growth receptor	Identifies subset	Variable	HER2-targeted therapy	[57]
Ki-67	Proliferation	Adjunct	High = aggressive	Supports grading	[58]

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CD68/CD163	Macrophage markers	Immune profiling	Emerging	Immunotherapy relevance	[59]
VEGF	Angiogenesis	Limited	Investigational	Anti-angiogenic relevance	[60]
β2-microglobulin	Immune-related	Refines profiling	Investigational	Immunotherapy context	[61]

4. Discussion

The present study combines descriptive bibliometric analysis with a focused literature review to provide a comprehensive overview of IHC studies investigating leptin and adiponectin in CRC. This dual approach enables both quantitative assessment of research activity and qualitative interpretation of the biological and clinical relevance of adipokine-related biomarkers. To the best of our knowledge, this is the first bibliometric analysis specifically addressing studies based on IHC evaluation of these two adipokines in CRC. Several parameters, such as annual publication output, core journals, and leading countries, have been analyzed. In addition, a detailed overview on the role of these hormones in CRC pathogenesis was presented.

The bibliometric findings indicate that research on leptin and adiponectin in CRC remains relatively limited in volume but demonstrates a clear upward trend, particularly after 2021. This increase reflects the growing recognition of metabolic and particularly obesity-related signaling pathways as critical factors in CRC development and progression [62]. It is well known fact that adipokines mediate obesity-induced inflammation in colorectal carcinogenesis [63].

It is noteworthy to mention that there is a significant difference in the number of publications between the Scopus and MEDLINE databases. The higher number of records indexed in Scopus suggests that bibliometric results in this field depend primarily on the choice of database, which could potentially lead to a systematic error in the assessment of scientific productivity. Therefore, future bibliometric studies should consider approaches involving multiple databases to ensure a more comprehensive representation of the scientific landscape.

Studies related to leptin showed a larger pool of publications and a slightly larger cluster of journals compared to studies related to adiponectin. This indicates that leptin has been investigated more extensively as a potential biomarker in CRC.

Additionally, geographical comparison of leptin and adiponectin datasets reveal several consistent patterns. China as the leading contributor in both research areas, particularly in Scopus-indexed literature. There is a strong representation from East Asia (China, Japan, and South Korea) across both adipokines. Substantial contribution from the USA also is observed, especially in Scopus. Increased international collaboration may therefore improve the robustness and external validity of future investigations.

However, no single country exceeds one-quarter of total output in larger datasets (Scopus), indicating that the field does not exhibit extreme geographic monopolization. Instead, the research landscape can be characterized as internationally distributed but regionally anchored in East Asia. In conclusion, the geographic bibliometric profile supports the idea that IHC research on leptin and adiponectin in CRC is internationally active. Regional concentration has been identified, but without any significant geographical centralization.

In summary, the overall bibliometric profile is characterized by a moderate research volume, high journal dispersion and oncology-centered publication landscape. All these findings indicate that research on the IHC expression of leptin and adiponectin in CRC remains highly specialized and fragmented field. There is no considerable consolidation in a small set of dedicated journals.

Beyond bibliometric patterns, the comprehensive literature review presented in this study demonstrated that leptin and adiponectin IHC-expression in CRC tissue may have potential prognostic value, especially in association with obesity and chronic inflammation. Both adipokines often present opposing biological roles in CRC [64,65].

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Leptin is consistently associated with pro-tumorigenic effects, including enhanced proliferation, angiogenesis, and metastatic potential. This adipokine acts primarily through signaling pathways such as JAK/STAT, PI3K/AKT/mTOR, and MAPK/ERK [18–22]. In contrast, adiponectin generally exerts anti-proliferative, anti-inflammatory, and pro-apoptotic effects. It operates via AMPK activation and downstream inhibition of mTOR signaling [25,26]. However, emerging evidence also indicates context-dependent and potentially pro-tumorigenic effects of adiponectin under specific microenvironmental and metabolic conditions [26,29]. All of this data underscores the complexity of adipokine signaling in CRC [63].

From a clinicopathological perspective, IHC studies demonstrate that increased expression of leptin and its receptor is frequently associated with advanced tumor stage, lymph node involvement, and poorer prognosis [30,33,34]. Conversely, reduced expression of adiponectin receptors correlates with more aggressive disease features, including metastasis and higher tumor grade [40,42]. These findings support the concept of a dysregulated leptin–adiponectin axis in CRC progression, where leptin upregulation and adiponectin pathway suppression jointly contribute to tumor aggressiveness [38]. Importantly, this complementary pattern suggests that combined assessment of these markers may provide greater prognostic value than evaluation of either adipokine alone [38].

When compared to established biomarkers for IHC analysis such as Ki-67, p53, CDX2, and mismatch repair (MMR) proteins in CRC, adipokines appear to provide additional insight into the metabolic aspects of tumor biology. While traditional markers primarily assess proliferation, differentiation, and genetic instability, leptin and adiponectin may detect microenvironmental changes associated with obesity and chronic inflammation [63]. Therefore, their inclusion in existing diagnostic panels could improve stratification of the patients.

Despite these promising aspects, several limitations should be considered. The main limitation of the current study is that the total number of identified publications was relatively low. This limits the robustness of trend analyses. In addition, the analysis was restricted to Scopus and MEDLINE, while publications indexed exclusively in other databases like Embase, Google Scholar etc. were not fully included. This may have led to potential underestimation of total research output. Additionally, few studies addressed standardized IHC scoring systems or combined leptin and adiponectin evaluation in large, multicenter cohorts. Future studies incorporating broader database coverage are warranted to provide a more comprehensive assessment of the evolving research landscape.

.5. Conclusions

In summary, the results of this study suggest that IHC research on leptin and adiponectin in colorectal malignancy represents a promising but still relatively underexplored scientific area. The increasing publication activity observed in recent years illustrates growing interest in the role of metabolic factors in CRC.

Combining these two adipokines with the routine assessment of molecular status would provide more precise diagnosis and stratification of patients. Standardization and larger prospective series will be needed before these adipokines become routine IHC markers in colorectal pathology.

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