World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(REVIEW ARTICLE)

Check for updates

Auricularia polytricha: A promising medicinal mushroom for combination therapy of colorectal cancer and understanding its potential mechanism of action

Gloria Claudia Kastanja [1], Aulia Rahmi Pawestri [2], Zahrah Firdaus [3], Felita Galih Perwita Sari [3], Michelle Anisa Ujianto [3], Khonsaa Aadilah [3], Elsafira Akrama Nabilahasna [3], Edwin Widodo [4], Eviana Norahmawati [5], Sofy Permana [6] and Agustina Tri Endharti [2, 7, *]

[1] *Bachelor Program of Medical, Faculty of Mathematics and Natural Sciences, Universitas Brawijaya, Indonesia.*
[2] *Department of Parasitology, Faculty of Medicine, Universitas Brawijaya, Indonesia.*
[3] *Master Program in Biomedical Sciences, Faculty of Medicine, Universitas Brawijaya, Indonesia.*
[4] *Department of Physiology, Faculty of Medicine, Universitas Brawijaya, Indonesia.*
[5] *Department of Pathology Anatomy, Faculty of Medicine, Universitas Brawijaya, Indonesia.*
[6] *Department of Biology, Faculty of Mathematics and Natural Sciences, Universitas Brawijaya, Indonesia.*
[7] *Biomedical Central Laboratory, Faculty of Medicine, Universitas Brawijaya, Indonesia.*

World Journal of Advanced Research and Reviews, 2023, 17(02), 365–377

Publication history: Received on 18 December 2022; revised on 29 January 2023; accepted on 31 January 2023

Article DOI: https://doi.org/10.30574/wjarr.2023.17.2.0152

Abstract

The Global Burden of Cancer (GLOBOCAN) revealed that there were 1,931,590 new cases and 935,173 deaths due to colorectal cancer in 2020. Treatment for colorectal cancer tends to be invasive and costly. Therefore, further research is needed on non-invasive complementary therapies that are safe and can be used to reduce the probability of recurrence in colorectal cancer patients at an affordable cost. The systematic literature review synthesized resources and presented them in a narrative review. Four databases, including PubMed, Research Gate, ProQuest, and Science Direct, were used to conduct the systematic reviews by following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) criteria. In this review, 36 articles were analyzed descriptively to help describe and summarize the data constructively. The results showed that complementary colorectal cancer therapy with *Auricularia polytricha* which contains active compounds, such as flavonoids, phenols, and beta-glucans, can increase the expression of miRNA-9, miRNA-217, miRNA-210, miRNA200c, and miRNA-132 which can improve the prognosis of colorectal cancer.

Keywords: Colorectal cancer; miRNA; *Auricularia polytricha;* Flavonoids; Phenol; Beta glucan

1. Introduction

The World Health Organization recorded 18.1 million cancer cases in the world with 9.6 million cancer mortalities in 2018 (WHO, 2018). These figures are expected to increase continuously. The Global Burden of Cancer (GLOBOCAN) revealed that there were 1,931,590 new cases and 935,173 deaths from colorectal cancer in 2020, of which 34,189 new cases arose from Indonesia. This prevalence is expected to rise continuously in the following years. Treatment for colorectal cancer is adjusted to the stage in each patient, with the most common treatment modality being surgery. However, surgery is an invasive treatment option due to the risk of infection, bleeding, and damage to structures around the incised area. Another therapeutic option, such as radiotherapy, also causes side-effects in patients, including distress, anxiety, depression, and fatigue [1]. In addition, the treatment costs of colorectal cancer are also high. Further study still is needed to explore complementary therapies that are safe and can be used to reduce the probability of recurrence in colorectal cancer patients.

* Corresponding author: Agustina Tri Endharti

Cancer treatment using natural compounds is now being widely discussed as one of the complementary cancer therapies. The therapeutic properties are stemming from the active compounds contained in these natural resources that have the potential as anti-cancer. One of the natural compounds that have been investigated for its role in complementary therapy for colorectal cancer is *Auricularia polytricha,* better known as the black ear mushroom , which contains flavonoids, polysaccharides, and phenols. [2].

In colorectal cancer, there is a down regulation of microRNAs (miRNAs), including miRNA-9, miRNA-217, miRNA-210, miRNA200c, and miRNA-1323. This down regulation leads to a poorer prognosis in colorectal cancer. I\On the other hand, increased expression of miRNA-9, miRNA-217, miRNA-210, miRNA-200c, and miRNA-132 might improve the prognosis of colorectal cancer [3]. The active compounds in *Auricularia polytricha,* including flavonoids, phenols, and polysaccharides, can increase the expression of miRNA-9, miRNA-217, miRNA-210, miRNA200c, and miRNA-132 [4]. Based on this rationale, the potential use of *Auricularia polytricha* needs to be investigated further to provide affordable complementary therapy for colorectal cancer in the future.

1.1. Black Ear Mushroom (Auricularia polytricha)

The black ear mushroom (*Auricularia polytricha*) has a shape resembling a human ear and the body shape is in the form of wavy, erratic, cup-shaped sheets. In general, the characteristics of black ear mushroom are soft jelly-like flesh, slimy, purplish or black fruit body, with a width of 6-10 cm. The black ear mushroom is a species of mushroom from the Heterobasidiomycetes class. This mushroom is generally used for consumption and various studies have been conducted to determine the biochemical activity of this mushroom, including as antitumor, anti-inflammatory, antihypertensive, anti-diabetic, anticoagulant, anti-oxidative, immune-modulatory, prebiotic, atherosclerosis treatment, and contains alkaloids and flavonoids which have potential as antimicrobials. Extract from black ear mushroom is also used for gastrointestinal cancer therapy [5].

Figure 1 Black Ear Mushroom (Auricularia polytricha) [2]

1.2. Taxonomic Classification of *Auricularia polytricha*

Kingdom: Fungi
Division: Basidiomycota
Class: Heterobasidiomycetes
Order: Auriculariales
Family: Auriculariacea
Genus: Auricularia
Species: *Auricularia polytricha*

2. Material and methods

This study is a systematic literature review which is synthesized in a narrative review. In conducting data searches, the authors optimized the data selection using inclusion and exclusion criteria. The inclusion criteria are: (1) the type of articles must be original research, review, or experimental research; (2) the topic must include colorectal cancer, microRNA, or the mushroom *Auricularia polytricha,* either separately or combined; (3) the articles were published in the last 10 years, between 2011-2021; (4) the articles are written in English, and (5) the articles are published from reputable and indexed publishers and indexed in SCOPUS, Web of Science, and SCImago Journal Rank.

The exclusion criteria include: 1) non-open access or articles with inaccessible full-texts; (2) articles that do not meet the quality assessment criteria based on Joanna Briggs Institute (JBI), namely not meeting at least 50% of the existing assessment criteria, which systematically assess the level of trust, relevance and results of published articles. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement is used in selecting the literature to be used. The PRISMA guidelines for systematic reviews define a process of study identification, screening, eligibility and inclusion and are outlined in Figure 2.

The research started by searching for keywords through pre-selected databases, including PubMed, Science Direct, and ResearchGate. Then, the data were processed by screening based on pre-determined inclusion and exclusion criteria. Furthermore, data extraction and analysis were carried out descriptively. Finally, the obtained data were synthesized into a literature review. Descriptive data analysis was performed to summarize the data in a constructive way (Table 1).

3. Results

3.1. Literature Selection

A literature review was conducted to investigate the effect of *Auricularia polytricha* extract on miRNA expression in colorectal cancer. Literature selection is carried out through four databases, including PubMed, Science Direct, ProQuest and ResearchGate, and processed using the evaluation criteria from JBI. Finally, the obtained article that were reviewed according to PRISMA. During the first stage, 150 articles were found, which, after deduplication, was reduced to 135 articles.

Using the predetermined inclusion and exclusion criteria, 90 articles were excluded (60 articles were not available in full texts and 30 articles did not meet the JBI criteria's for both systematic review and original articles). After an eligibility assessment is carried out, nine articles did not meet the eligibility requirements because they originated from not indexed or non-reputable publishers, bringing a total of 36 articles to be included in the data synthesis (Figure 2)

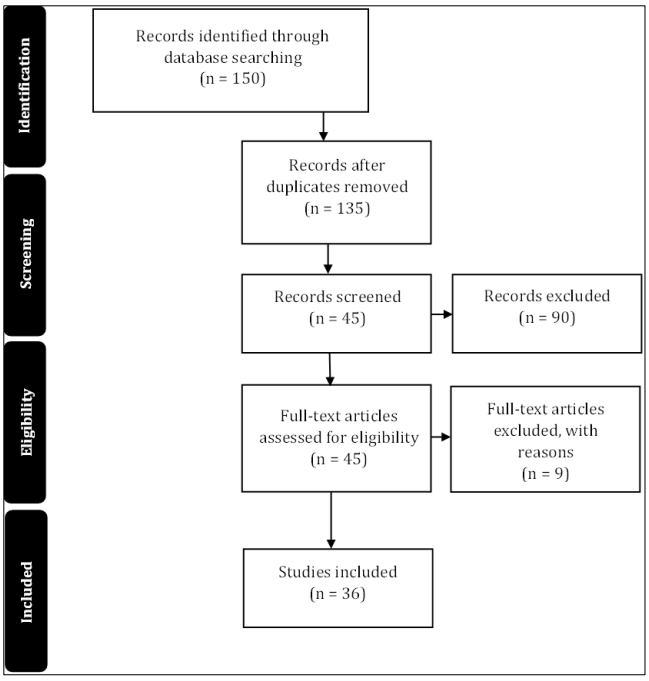

Figure 2 Flowchart of Literature Selection

3.2. Evaluation of Literature Quality

The evaluation literature quality was performed using instruments provided by JBI. The JBI criteria assessment is detailed and adjustable to the research design of the selected articles of either systematic review or original article (Table 1).

Table 1 JBI's Criteria for Systematic Review and Original Articles

No	JBI Criteria for Systematic review	JBI Criteria for Original Articles
1.	Is the review question clearly and explicitly stated?	Is it clear in the study what is the 'cause' and what is the 'effect'
2.	Were the inclusion criteria appropriate for the review question?	Were the participants included in any comparisons similar?
3.	Was the search strategy appropriate?	Was there a control group?
4.	Were the sources and resources used to search for studies adequate?	Were the outcomes of participants included in any comparisons measured in the same way?
5.	Were the criteria for appraising studies appropriate?	Were outcomes measured in a reliable way?
6.	Were the methods used to combine studies appropriate?	Was appropriate statistical analysis used?
7.	Was the likelihood of publication bias assessed?	
8.	Were recommendations for policy and/or practice supported by the reported data?	
9.	Were the specific directives for new research appropriate?	

3.3. Analysis of Critical Appraisal

After conducting a quality assessment using the criteria from JBI both for *Systematic Review* and original articles, 36 articles were found to be feasible for further systematic review (Table 2). These articles contained the active compounds in *Auricularia polytricha* and their relationship to miRNA expression affecting colorectal cancer. They consisted of 19 articles about the active compounds of flavonoids, 8 articles about phenol, and 8 articles about β-glucan.

Table 2 *In vitro* and *In vivo* Studies of Auricularia polytricha and their Phytochemicals with Anti-Colonic Cancer Properties

Active Compounds	Author, Year, Country	Research design	Research subject	Research result	Ref.
Flavonoids	Packilakshmi *et al.*, 2016, India	Experimental, *In vitro*	*Auricularia polytricha* extract from dried fruiting bodies from Hangzhou, China	*Auricularia polytricha* exhibited antioxidative activities. Secondary metabolites of phenols and flavonoids could be observed in extracts of *Auricularia polytricha.*	[2]
	Chen *et al.*2015, Taiwan	Systematic Review	Seven active compounds of flavonoids (EGCG, galangin, quercetin, baicalein, oroxylin, genistein, siblinin) which provide biological functions in hepatocellular carcinoma	Flavonoids showed various chemo-preventive effects, either singly or in combination, against the causes of hepatocellular carcinoma.	[6]
	Nik Salleh *et al.*, 2020, Malaysia	Systematic Review	*In vitro* and in vivo studies of baicalein extracted from *Oroxylum indicum*	Baicalein extracted from the *Oroxylum indicum* demonstrated anti-cancer, anti-bacterial, anti-hyperglycemia,	[7]

				neurogenesis, cardioprotective, anti-adipogenesis, anti-inflammatory properties, and played a role in wound healing.	
	Li Yang *et al.*, 2019, China	Experimental, *In vitro*	NIH/3T3 cell line	Baicalein inhibited cell proliferation and collagen production by regulating the miRNA-9/IGF-1 axis via NF-kB and Wnt/β-catenin signaling pathways.	[3]
	Park *et al.*, 2016, Korea	Experimental, *In vitro*	60 colorectal cancer tissues from the Chonbuk National University Hospital Biobank, Korea	TM4SF1 expression was increased in colorectal cancer and associated with tumor staging and lymph node metastasis.	[8]
	Lin *et al.*, 2016, China	Experimental, *In vitro*	Human EOC OVCAR-3 cell line	MiRNA-9 acted as a promising tumor inhibitor for ovarian cancer by targeting the SDF-1/CXCR4 pathway.	[9]
	Afsane *et al.*, 2021, Iran	Systematic Review	Gastrointestinal cancer	MiRNA-9 had a role in tumor suppression and down-regulation in colorectal cancer.	[10]
	Kim *et al.*, 2020, Korea	Experimental, *In vitro*	357 tumor tissue specimens obtained from colorectal cancer patients post-surgery and 113 fresh whole blood samples	Low miRNA-9 expression were associated with colorectal cancer clinical parameters, including lymph node metastases, clinical stage, and survival.	[11]
	Zhang *et al.*, 2015, China	Experimental, *In vitro*	Human osteosarcoma 143B cells	5μg/mL quercetin increased cisplatin sensitivity by modulating the miRNA-217-KRAS.	[12]
	Hashemzaei *et al.*, 2017, Iran	Experimental, *In vitro* and in vivo	9 cancer cells: CT-26, PC-12, LNCaP, PC-3, MOLT-4, U266B1, Raji, MCF-7, and CHO cells. Mice implanted with CT-26 and MCF-7 cells.	The inhibitory effect of quercetin on cancer cell growth was dose- and time-dependent. In vivo studies showed that quercetin significantly reduced tumor volume and increase the survival rate of animals.	[13]
	Parisa *et al.*, 2021, Iran	Systematic Review	Osteosarcoma cells	Quercetin operated various mechanisms to prevent osteosarcoma progression, thus having the potential to become part of osteosarcoma management.	[14]
	Qi *et al.*, 2019, China	Experimental, in vivo	48 C57BL/6J 6-week-old mice	β-glucan and quercetin consumption reduced colon	[15]

				damage and mortality in CRC rats (12.5%).	
	Zhang *et al.*, 2016, China	Experimental, *In vitro*	Malignant cell lines: RKO and SW480	MiRNA-217 inhibited tumor growth and triggered apoptosis in colorectal cancer. This was related to the downregulation of MAPK signaling.	[16]
	Wang *et al.*, 2015, China	Experimental, in vivo and *In vitro*	In vivo: BALB/c-nude *mice* aged 4 weeks *In vitro*: tissue samples taken from patients undergoing coloprotectomy	MiRNA-217 expression was negatively correlated with astrocyte elevated gene-1 (AEG1) expression which increased the proliferation and invasion of colorectal cancer cells.	[4]
	Flum *et al.*, 2018, Germany	Experimental, *In vitro*	HCT 116, T98G, HT-29, SW480, SKOV3, and HEK293T cells	MiRNA-217 increased apoptosis of colorectal cancer cells by targeting PRKCI, BAG3, ITGAV, and MAPK1 via ERK-MAPK signaling pathways.	[17]
	Yu *et al.*, 2017, China	Experimental, *In vitro*	21 pairs of colorectal specimens, 21 human colorectal adenocarcinoma cancer, and 28 adjacent tissues	MiRNA-217 inhibited colorectal cancer cell proliferation by targeting TCF7L2 through the WNT/β-catenin signaling pathway.	[18]
	Chen *et al.*, 2020, China	Experimental, *In vitro*	Human cell cancer lines (H1299 and A549) and primary immortalized bronchial epithelial cell line (BEAS2B)	EGCG and nano-EGCG inhibited the growth of H1299 lung cancer line with half-maximal inhibitory concentration (IC50) of 36.03 and 4.71 µm.	[19]
	Qiu *et al.*, 2015, China	Experimental, *In vitro*	Human bone marrow-derived mesenchymal stem cells	Treatment with EGCG increased miRNA-210 in mesenchymal stem cells by targeting the 3` UTR of EFNA3.	[20]
	Kim *et al.*, 2013, Korea	Experimental, *In vitro*	Adipose-derived stem cells isolated from lipo-aspirated subcutaneous tissue	Reactive oxygen species generation from different sources induced miRNA-210 expression in adipose-derived stem cells via PDGFR-β, Akt, and ERK pathways.	[21]
	Tagscherer *et al.*, 2016, Germany	Experimental, *In vitro*	HCT116, SW480, and SW707 colorectal cancer cell lines	MiRNA-210 initiated apoptosis in colorectal cancer cells through a ROS-independent mechanism.	[22]
phenol	Packilakshmi *et al.*, 2016, India	Experimental, *In vitro*	*Auricularia polytricha* extract from dried fruiting	*Auricularia polytricha* exhibited antioxidative activities. Secondary	[2]

			bodies from Hangzhou, China	metabolites of phenols and flavonoids could be observed in extracts of *Auricularia polytricha.*	
	Preethi *et al.*, 2016, India	Systematic Review	Cancer patients in general	Phenol played a role in inhibiting the proliferation and migration of cancer cells.	[23]
	Abotaleb *et al.*, 2020, Doha	Systematic Review	Various plants containing phenolic acids	Phenols were strong candidates in the treatment of various types of cancer, acting on proliferation, angiogenesis, growth, and differentiation, metastasis, and apoptosis.	[24]
	Al-Rimawi *et al.*, 2016, Palestine	Systematic Review	HOS and KHOS human osteosarcoma cell lines	The total phenolic content, total flavonoid content, and antioxidant activity of *Tragopogon porrifloius* plants showed anticancer activities against KHOS cancer line.	[25]
	Zhang *et al.*, 2020, China	Experimental, *In vitro*	Human ovarian cancer cell line (OVCAR-3)	Garcinol significantly decreased PI3K and AKT protein phosphorylation and down regulated NF-kB expression. Garcinol has the potential to be used as an anticancer agent and can synergize with the effects of DDP/cisplatin.	[26]
	Huang *et al.*, 2015, Taiwan	Experimental, *In vitro*	Human pancreatic cancer cell lines	Treatment with garcinol suppressed self-renewal ability, reduced metastatic potential, and increased drug sensitivity in pancreatic cancer cells.	[27]
	Liu *et al.*, 2014, China	Experimental, *In vitro*	Human bladder cell lines (UMUC-3 and T24)	MiRNA-200c controlled the EMT process through BMI-1 in *bladder cancer cells*, and it inhibits its proliferation through down-regulation of E2F3. MiRNA-200c targets include BMI-1 and E2F3 as regulators of EMT and proliferation.	[28]
	Song *et al.*, 2015, China	Experimental, in vivo and *In vitro*	In vivo: BALC/c mice *In vitro*: human breast cancer cell line (4T1)	MiRNA-200c acted as a tumor suppressor in breast cancer through inhibition of KRAS translation in in vivo and *In vitro*.	[29]

polysaccharides	Song and Du, 2012, China	Experimental, *In vitro*	*Auricularia polytricha* from a local market in Hangzhou, China	The water-soluble β-glucan structure was obtained from the fruiting bodies of the mushroom *Auricularia polytricha* by combined separation using high-speed countercurrent chromatography (HSCCC)-Sephacryl S-300 HR column chromatography.	[30]
	Xu *et al.*, 2016, China	Experimental, in vivo and *In vitro*	In vivo: mice sarcoma S-180 tumor models *In vitro*: S-180 and human cervical carcinoma cells (HeLa)	LNT, which is a β-(1,3)-glucan with a β-(1,6) branch of the fruiting bodies *Lentinus edodes*, showed significant inhibitory activity against S-180 tumor growth in mice, LNT inhibited the proliferation/viability of S-180 and HeLa cells.	[31]
	Qi *et al.*, 2019, China	Experimental, in vivo	48 C57BL/6J 6-week-old mice	Alternating β-glucan and quercetin consumption reduced colon damage and mortality in CRC rats, with a 12.5% reduction in mortality.	[15]
	Alina *et al.*, 2013, Finland	Experimental, *In vitro*	Primary human macrophages	β -glucan increased the expression of miRNA-29b1-5p, miRNA-132, miRNA-146a, miRNA-155, and miRNA-212.	[32]
	Meysam *et al.*, 2021, Iran	Systematic Review	Cancer cell lines	MiRNA-132 played a role in tumor progression through regulation of PI3K/AKT and MAPK signaling pathways.	[33]
	Li *et al.*, 2015, China	Experimental, *In vitro* and in vivo	*In vitro*: human lung adenocarcinoma cell line (A549), lung squamous carcinoma cell line (YTMLC-9), lung large carcinoma (H460), and normal human bronchial epithelial cells In vivo: nude mice	MiRNA-132 could be a therapeutic target in human lung cancer.	[34]
	Liu *et al.*, 2015, China	Experimental, *In vitro* and in vivo	*In vitro*: 40 pairs of human HCC tissues and pairs of non-cancerous liver tissues obtained from patients undergoing liver resection In vivo: 20 BALB/C/-nu/nu nude male mice	MiRNA-132 expression was decreased in HCC cell and its expression level was related to tumor differentiation.	[34]
	Zheng *et al.*, 2014, China	Experimental, *In vitro*	CRC tissues with distant metastases (n=32) and without distant metastases	MiRNA-132 played a critical role in colorectal	[35]

			(n=30), HT-29, HCT116, SW480, SW620 and LoVo CRC, 293T embryonic kidney and NCM460 cell lines	cancer invasion and metastasis.	

3.4. The active compounds of *Auricularia polytricha* are potential effects against colorectal cancer

Flavonoids are a group of secondary plant metabolites composed of various classes of polyphenolic compounds found in fruits, vegetables, roots, stem, flower, and nuts, as well as beverages such as tea and wine, which can be consumed every day. Flavonoids are divided into seven compounds, including flavanol, flavanone, flavone, isoflavones, flavonols, anthocyanins, and flavonolignans [6]. *Auricularia polytricha* extract was reported to contain secondary metabolites of phenol and flavonoids [2].

Quercetin is flavonoids which enter in class flavonols, quercetin show anticancer activity both *In vitro* and in vivo [13]. Quercetin put in place various mechanisms to prevent progression osteosarcoma [14]. Quercetin able to increase the sensitivity in osteosarcoma cells by modulating the miRNA-217-KRAS. miRNA-217 is tumor suppressors which increase apoptosis and proliferation as well as metastases cell osteosarcoma [12]. miRNA-217 inhibit tumor growth and trigger apoptosis on colorectal cancer. This related with down regulation from MAPK signaling pathways [16] .

Epigallocatechin gallate (EGCG) is a flavonoid classified in the flavanol class. EGCG and nano-EGCG in low dosages was reported to significantly hinder proliferation, colony formation, migration, and invasion of human lung cancer cells through the activation of the AMPK signaling pathway [19]. EGCG showed protective effects by responding to hypoxia and promote roles of osteogenic differentiation on mesenchymal stem cells by increasing miRNA-210 [20].

The structure of β-glucan, which is water soluble with a molecular weight of 1.62×10^5 M, are derived from the fruiting bodies of *Auricularia polytricha* through a combined separation of high-speed countercurrent chromatography (HSCCC) - *Sephacryl S-S-300* HR column chromatography [30]. LNT is a β-glucan derived from *Lentinus edodes* which showed antitumor effects [31]. Alternate consumption of β-glucan and quercetin was shown to reduce colon damage and mortality by 12.5% in rat models with colorectal cancer [15].

MiRNA-9 is down-regulated in colorectal cancer and played important role in cancer invasion and metastatic through the regulation of TM4SF1 expression [8]. MiRNA-9 could act as a promising tumor inhibitor for ovarian cancer by targeting the SDF- 1/CXCR4 pathway [9]. The tumor suppression functions of miRNA-9 and miRNA-9 was down-regulated in colorectal cancer [10]. Chrysin, as flavones, demonstrated cancer chemo-preventive activity via miRNA-9 and Let-7a [11].

MiRNA-217 is a tumor suppressor which increases apoptosis and inhibits proliferation and metastases in osteosarcoma cells [12]. MiRNA-217 inhibited tumor growth and induced apoptosis in colorectal cancer and was related to the down regulation of MAPK signaling [16] .

MiRNA- 217 increased apoptosis in colorectal cancer cells by targeting PRKCI, BAG3, ITGAV, and MAPK1 through the ERK- MAPK signaling pathways [17]. MiRNA-217 inhibited the proliferation of colorectal cancer cells by targeting TCF7L2 through the WNT/β-catenin signaling pathways [18].

EGCG showed protective effect to events of hypoxia and promoted osteogenic differentiation in mesenchymal stem cells by increasing miRNA-210 expression [20]. Reactive oxygen species (ROS) generation from different sources induced miRNA-210 expression on adipose-derived stem cells via PDGFR-β, Akt and ERK pathways [21]. MiRNA-210 initiated apoptotic events in colorectal cancer cells through ROS-independent mechanism [22].

MiRNA-200c controlled the EMT process through BMI-1 on bladder cancer cells, and inhibited its proliferation through down-regulation of E2F3. Targets of miRNA-200c included BMI-1 and E2F3, which are EMT regulators [28]. MiRNA-200c also acted as a tumor suppressor on breast cancer through KRAS translation in an in vivo and *In vitro* study [29].

MiRNA-132 played role in tumor progression through the regulation of PI3K/AKT and MAPK signaling pathways [33]. MiRNA-132 expression was decreased in studies on lungs cancer cells. Furthermore, it was found that miRNA-132 significantly inhibited lung cancer migration and invasion *In vitro*. In addition, miRNA-132 overexpression could also inhibit tumor growth in mice, thus miRNA-132 could be a target therapy for lung cancer in humans [34]. miRNA-132

inhibited cell proliferation, colony formation, migration, and invasion to induce apoptosis and cell cycle arrest at the G0/G1 stage *In vitro*, while also suppressing tumor growth in vivo. MiRNA-132 overexpression inhibited PIK3R3 expression and activated ACT/mTOR signaling pathways [34].

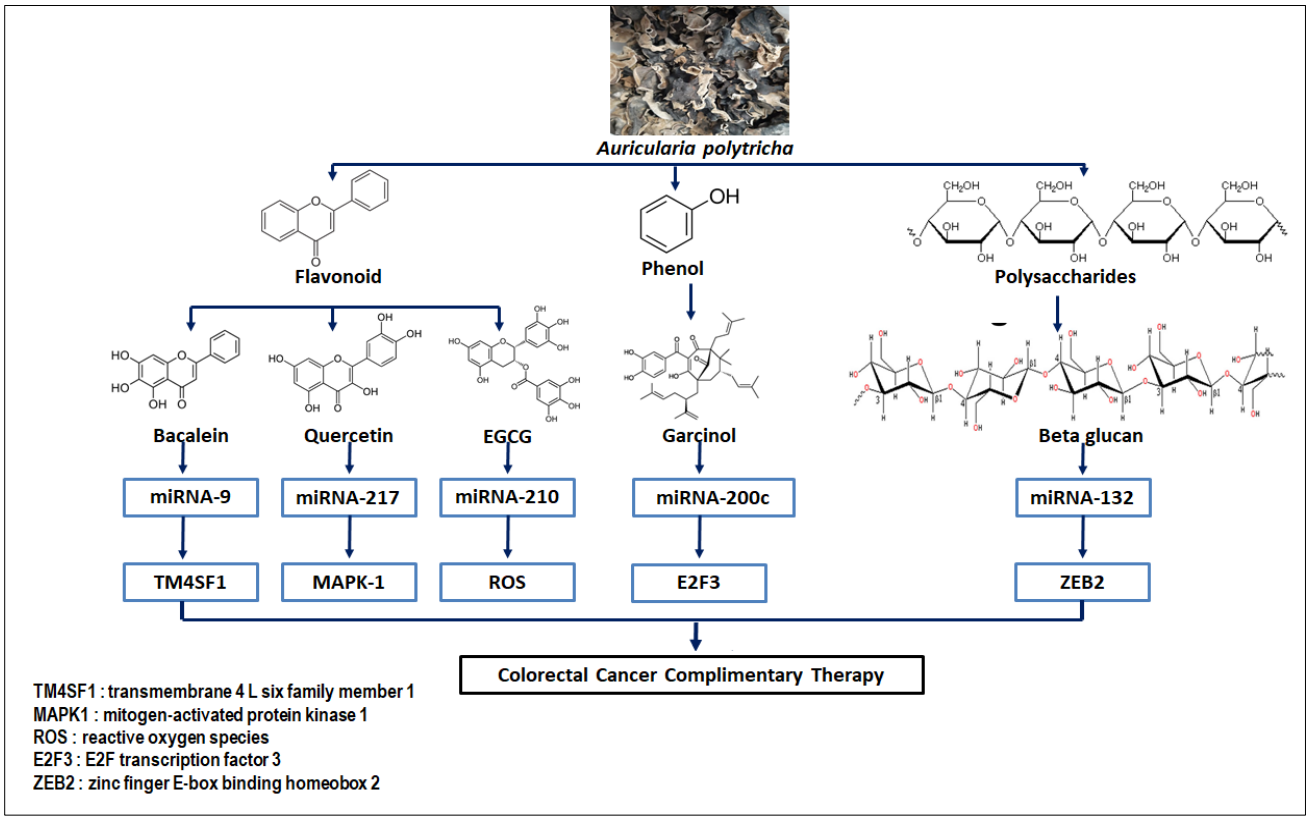

Figure 3 Anti-cancer Activities of *Auricularia polytricha* and their Mechanism of Action

4. Discussion

Colorectal cancer commonly manifests in the large intestine in the colon and/or rectum and its development is affected by external and internal factors, such as environmental factors, heterozygosity, and microsatellite instability [36]. Previous studies have shown that miRNA plays a role in colorectal carcinogenesis, cancer progression, and influences the incidence of metastasis [37].

Auricularia polytricha contains an active compound known as flavonoid that has antitumor properties [2]. Based on their molecular structure, flavonoids are divided into seven classes, such as flavanols, flavanones, flavones, isoflavones, flavonols, anthocyanins, and flavonolignans. Flavonoids are bioactive components with various health benefits, including antioxidants and miRNA's target in cancer pathogenesis [38]. Besides, when used alone or in combination, they widely provided chemo-preventive effects. [6].

Baicalein, a part of flavonoid, had shown anti-cancer properties and inhibited cell proliferation and collagen production by regulating the miRNA-9/IGF-1 through the NF-kB and Wnt/β-catenin signaling pathways [3, 6]. The tumor suppression function in miRNA-9 and miRNA-9 were downregulated in colorectal cancer [10]. The regulation of TM4SF1 expression, miRNA-9 played an important role in colorectal cancer invasion and metastasis [8].

Subsequently, quercetin is a flavonol-classed flavonoid exhibiting anticancer activities both *In vitro* and in vivo [6, 13]. Quercetin was able to modulate the miRNA-217-KRAS axis, in which miRNA-217 inhibited tumor growth and induced apoptosis in colorectal cancer causing the downregulation of the MAPK signaling pathway [4, 16]. MiRNA-217 elevated colorectal cancer cell apoptosis by targeting PRKCI, BAG3, ITGAV, and MAPK1 via ERK-MAPK signaling pathways, as well inhibited the proliferation of colorectal cancer cells in the WNT/β-catenin signaling pathway by targeting TCF7L2 [17, 18].

Furthermore, low doses of EGCG, a flavonoid of the flavanol class, was able to significantly inhibit the proliferation, colony formation, migration, and invasion of human lung cancer cells through the activation of the AMPK signaling pathway [6, 19]. EGCG showed an increase in miRNA-210 as a protective effect against osteogenic differentiation in mesenchymal stem cells [20]. Through PDGFR-β, Akt, and ERK pathways, ROS were generated from different sources, inducing miRNA-210 expression in adipose-derived stem cells that were able to initiate apoptosis in colorectal cancer cells through a ROS-independent mechanism [21, 22].

Phenol in *Auricularia polytricha* acted on various molecular targets (proliferation, angiogenesis, growth and differentiation, metastasis and apoptosis), and inhibited the proliferation and migration of cancer cells [2, 23, 24]. Encompassed with structures of the phenolic hydroxyl group, garcinol had the potential to be used as an anticancer agent [26]. MiRNA-200c controlled EMT processing via BMI-1 in cancer cells of the bladder, inhibiting their proliferation through down-regulation of E2F3 and acted as a tumor suppressor in breast cancer through inhibition of KRAS translation in vivo and *In vitro* [28, 29].

AAPS-1 is a water-soluble β-glucan structure with a molecular weight of 1.62×10^5 Da, from the fruiting bodies of *Auricularia polytricha*, when separated using a combination of high-speed countercurrent chromatography (HSCCC)-Sephacryl S-S-300 HR column chromatography [30]. Beta-glucan elevated the expression of miRNA-29b1-5p, miRNA-132, miRNA-146a, miRNA-155, and miRNA-212 [32]. MiRNA-132 was down regulated in colorectal cancer with distant metastases, with possible disease-free survival and distant metastases in colorectal cancer patients. ZEB2 as the EMT regulator was a target of miRNA-132 that could be used as prognostic indicator and therapeutic target of colorectal cancer [35].

The active compounds in *Auricularia polytricha* showed a potential as a complementary therapy for colorectal cancer, to regulate the expression of certain miRNAs, working through pathways affecting the proliferation and apoptosis of colorectal cancer cells. Findings regarding the association of the active compounds could be a point of interest for researchers, healthcare practitioners, and pharmaceutical companies to develop complementary therapies that are more accessible and effective. In addition, the results of this systematic review can be used as a reference in biomedical science for the optimized use of natural compounds.

5. Conclusion

Auricularia polytricha showed potential benefits as an anticancer agent through its active compounds. From various literatures, at least three active compounds displayed anti-cancer functions, such as flavonoids, phenols, and β-glucan. These compounds held different roles in miRNA regulation, such as miRNA-9, miRNA-217, miRNA-210, miRNA-200c, and miRNA-132, since these miRNAs function directly to either increase or inhibit the activity of certain pathways that affect the proliferation and apoptosis of colorectal cancer cells.

Compliance with ethical standards

Acknowledgments

The authors would like to thank Faculty of Medicine, Universitas Brawijaya, Malang for supporting us.

Disclosure of conflict of interest

The authors declare there is no conflict of interest.

References

[1] Dilalla V, Chaput G, Williams T, et al. Radiotherapy side effects: Integrating a survivorship clinical lens to better serve patients. *Curr Oncol* 2020; 27: 107–112.

[2] Packialakshmi B, Sudha G, Charumathy M. Total phenol, flavonoid and antioxidant properties of auricularia auricula-judae. *Int J Pharm Pharm Sci* 2015; 7: 233–237.

[3] Yang L, Li X, Zhang S, et al. Baicalein inhibits proliferation and collagen synthesis of mice fibroblast cell line NIH/3T3 by regulation of miRNA-9/insulin-like growth factor-1 axis. *Artif Cells, Nanomedicine Biotechnol* 2019; 47: 3202–3211.

[4] Wang B, Shen ZL, Jiang KW, et al. MicroRNA-217 functions as a prognosis predictor and inhibits colorectal cancer cell proliferation and invasion via an AEG-1 dependent mechanism. *BMC Cancer* 2015; 15: 1–11.

[5] Rahmawati S. Jamur Sebagai Obat. *J Agroindustri Halal* 2015; 1: 14–24.

[6] Liao CY, Lee CC, Tsai CC, et al. Novel investigations of flavonoids as chemopreventive agents for hepatocellular carcinoma. *Biomed Res Int*; 2015. Epub ahead of print 2015. DOI: 10.1155/2015/840542.

[7] Salleh NNHN, Othman FA, Kamarudin NA, et al. The Biological Activities and Therapeutic Potentials. *Molecules* 2020; 25: 1–23.

[8] Park YR, Lee ST, Kim SL, et al. MicroRNA-9 suppresses cell migration and invasion through downregulation of TM4SF1 in colorectal cancer. *Int J Oncol* 2016; 48: 2135–2143.

[9] He L, Zhang L, Wang M, et al. miRNA-9 functions as a tumor inhibitor of cell proliferation in epithelial ovarian cancer through targeting the SDF-1/CXCR4 pathway. *Exp Ther Med* 2017; 13: 1203–1208.

[10] Bahrami A, Jafari A, Ferns GA. The dual role of microRNA-9 in gastrointestinal cancers: oncomiRNA or tumor suppressor? *Biomed Pharmacother* 2022; 145: 112394.

[11] Kim H, Kim T, Jaygal G, et al. Downregulation of miRNA-9 correlates with poor prognosis in colorectal cancer. *Pathol Res Pract* 2020; 216: 153044.

[12] Zhang X, Guo Q, Chen J, et al. Quercetin enhances cisplatin sensitivity of human osteosarcoma cells by modulating microRNA-217-KRAS axis. *Mol Cells* 2015; 38–38: 638–642.

[13] Hashemzaei M, Far AD, Yari A, et al. Anticancer and apoptosis-inducing effects of quercetin *In vitro* and in vivo. *Oncol Rep* 2017; 38: 819–828.

[14] Maleki Dana P, Sadoughi F, Asemi Z, et al. Anti-cancer properties of quercetin in osteosarcoma. *Cancer Cell Int* 2021; 21: 1–9.

[15] Qi J, Yu J, Li Y, et al. Alternating consumption of β-glucan and quercetin reduces mortality in mice with colorectal cancer. *Food Sci Nutr* 2019; 7: 3273–3285.

[16] Zhang N, Lu C, Chen L. MiRNA-217 regulates tumor growth and apoptosis by targeting the MAPK signaling pathway in colorectal cancer. *Oncol Lett* 2016; 12: 4589–4597.

[17] Flum M, Kleemann M, Schneider H, et al. miRNA-217-5p induces apoptosis by directly targeting PRKCI, BAG3, ITGAV and MAPK1 in colorectal cancer cells. *J Cell Commun Signal* 2018; 12: 451–466.

[18] Yu B, Ye X, Du Q, et al. The long non-coding RNA CRNDE promotes colorectal carcinoma progression by competitively binding miRNA-217 with TCF7L2 and enhancing the Wnt/β-catenin signaling pathway. *Cell Physiol Biochem* 2017; 41: 2489–2502.

[19] Chen BH, Hsieh CH, Tsai SY, et al. Anticancer effects of epigallocatechin-3-gallate nanoemulsion on lung cancer cells through the activation of AMP-activated protein kinase signaling pathway. *Sci Rep* 2020; 10: 1–11.

[20] Qiu Y, Chen Y, Zeng T, et al. EGCG ameliorates the hypoxia-induced apoptosis and osteogenic differentiation reduction of mesenchymal stem cells via upregulating miRNA-210. *Mol Biol Rep* 2016; 43: 183–193.

[21] Kim JH, Park SG, Song SY, et al. Reactive oxygen species-responsive miRNA-210 regulates proliferation and migration of adipose-derived stem cells via PTPN2. *Cell Death Dis* 2013; 4: e588-14.

[22] Tagscherer KE, Fassl A, Sinkovic T, et al. MicroRNA-210 induces apoptosis in colorectal cancer via induction of reactive oxygen. *Cancer Cell Int* 2016; 16: 1–12.

[23] Anantharaju PG, Gowda PC, Vimalambike MG, et al. An overview on the role of dietary phenolics for the treatment of cancers. *Nutr J* 2016; 15: 1–16.

[24] Abotaleb M, Liskova A, Kubatka P, et al. Therapeutic potential of plant phenolic acids in the treatment of cancer. *Biomolecules* 2020; 10: 1–23.

[25] Al-Rimawi F, Rishmawi S, Ariqat SH, et al. Anticancer Activity, Antioxidant Activity, and Phenolic and Flavonoids Content of Wild Tragopogon porrifolius Plant Extracts. *Evidence-based Complement Altern Med*; 2016. Epub ahead of print 2016. DOI: 10.1155/2016/9612490.

[26] Zhang J, Fang H, Zhang J, et al. Garcinol Alone and in Combination With Cisplatin Affect Cellular Behavior and PI3K/AKT Protein Phosphorylation in Human Ovarian Cancer Cells. *Dose-Response* 2020; 18: 1–11.

[27] Huang C-C, Lin C-M, Huang Y-J, et al. Garcinol downregulates Notch1 signaling via modulating miRNA-200c and suppresses oncogenic properties of PANC-1 cancer stem-like cells. *Biotechnol Appl Biochem* 2015; 1–21.

[28] Liu L, Qiu M, Tan G, et al. Correction to: miRNA-200c Inhibits invasion, migration and proliferation of bladder cancer cells through down-regulation of BMI-1 and E2F3 (Journal of Translational Medicine, (2014), 12, 1, (305), 10.1186/s12967-014-0305-z). *J Transl Med* 2022; 20: 1–10.

[29] Song C, Liu LZ, Pei XQ, et al. miRNA-200c inhibits breast cancer proliferation by targeting KRAS. *Oncotarget* 2015; 6: 34968–34978.

[30] Song G, Du Q. Structure characterization and antitumor activity of an α β-glucan polysaccharide from Auricularia polytricha. *Food Res Int* 2012; 45: 381–387.

[31] Xu H, Zou S, Xu X, et al. Anti-Tumor effect of β-glucan from Lentinus edodes and the underlying mechanism. *Sci Rep* 2016; 6: 1–13.

[32] Poltajainen A, Matikainen S, Nyman T, et al. 199: Beta-glucan inducible microRNAs negatively regulate

[33] Moghbeli M, Zangouei AS, Nasrpour Navaii Z, et al. Molecular mechanisms of the microRNA-132 during tumor progressions. *Cancer Cell Int* 2021; 21: 1–11.

[34] Li Y, Zu L, Wang Y, et al. miRNA-132 inhibits lung cancer cell migration and invasion by targeting SOX4. *J Thorac Dis* 2015; 7: 1563–1569.

[35] Zheng Y Bin, Luo HP, Shi Q, et al. miRNA-132 inhibits colorectal cancer invasion and metastasis via directly targeting ZEB2. *World J Gastroenterol* 2014; 20: 6515–6522.

[36] Mitry E, Fields ALA, Bleiberg H, et al. Adjuvant chemotherapy after potentially curative resection of metastases from colorectal cancer: A pooled analysis of two randomized trials. *J Clin Oncol* 2008; 26: 4906–4911.

[37] Schetter AJ, Okayama H, Harris CC. The Role of microRNAs in Colorectal Cancer. *Cancer J* 2011; 23: 1–7.

[38] Singh S, Raza W, Parveen S, et al. Flavonoid display ability to target microRNAs in cancer pathogenesis. *Biochem Pharmacol* 2021; 189: 114409.