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REVIEW ARTICLE

Investigating the Effect of Eugenol on Regulating the Inflammatory Pathways under the Control of miR-223-3p in the Glioblastoma

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KEYWORDS

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ABSTRACT: MicroRNA-223 (miR-223) has become a significant regulator in various biological processes, particularly in gliomas and inflammatory responses. Research indicates that miR-223 is crucial in modulating drug resistance in glioma stem cells (GSCs), particularly in response to temozolomide (TMZ) treatment. Elevated levels of miR-223 correlate with increased chemoresistance, linked to the downregulation of PAX6 and activation of the PI3K/AKT signaling pathway. Conversely, overexpression of miR-223 enhances the sensitivity of glioblastoma (GBM) cells to radiation-induced apoptosis, suggesting it is an impending therapeutic target. Additionally, miR-223 is connected with epithelial-mesenchymal transition (EMT) in GBM, promoting invasive properties and correlating with the expression of metalloproteinases and vascular endothelial growth factor (VEGFA). In the context of inflammation, miR-223 regulates immune cell functions by targeting NLRP3, a key component of the inflammasome, thereby influencing neutrophil and macrophage activity. Its role in mitigating acute lung injury and liver failure by inhibiting NET formation further underscores its importance in inflammatory diseases. Overall, miR-223 represents a dual-function molecule with implications in cancer progression and inflammatory responses, highlighting its potential as a biomarker and healing objective in gliomas and related conditions. Overall, the findings suggest that both eugenol and miR-223 play significant roles in glioblastoma biology, offering avenues for further research and potential therapeutic interventions.

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INTRODUCTION

The serious character of microRNAs (miRNAs) in the expansion and progression of cancer has become increasingly evident in recent research. Numerous factors—including stress, environmental influences, epigenetic changes, genetic alterations, and pharmacological treatments—contribute to the dysregulation of miRNAs in cancerous cells. Advances in miRNA profiling databases, the extraction of RNA from difficult samples, and the implementation of innovative high-throughput gene expression techniques, such as DNA microarrays and RNA sequencing, have significantly advanced the study of miRNAs in cancer[1]. Researches demonstrate that miRNA expression differs among cancers, helping to clarify the molecular mechanisms that contribute to their dysregulation. Moreover, it is becoming more apparent that the roles of miRNAs as oncogenes and tumor suppressors in different cancers are, to some extent, associated with gene expression patterns that are specific to particular tissues. Enhancements survival rates, reduction in tumor growth, and prevention of metastasis in cancer patients can be achieved through two strategies: (i) silencing oncogenic miRNAs to promote the expression of tumor suppressor genes, and (ii) overexpressing tumor-suppressive miRNAs to inhibit oncogene expression. Additionally, miRNAs are integral to the development of chemoresistance in various cancer types. Importantly, adjusting miRNA expression in patients who experience relapse may hinder cancer progression and increase the responsiveness of cancer cells to targeted pharmacological therapies[2].

Glioblastoma (GB) represents the greatest prevalent form of malignant brain tumors, accounting for 50.1% of cases. Although the annual incidence remains relatively low, estimated at approximately 3.19 per 100,000 individuals in developed nations, there appears to be a rising trend in certain countries[3]. This increase may be attributed to factors such as an aging population and advancements in diagnostic techniques. The median age at which individuals are diagnosed with GB is around 64 years, with incidence rates escalating with age, peaking at 15 per 100,000 individuals in the age group of 75 to 84 years[4].

So, we will briefly discuss the role of miR-223-3p in the antioxidant and anti-inflammation effect in cooperation with eugenol, while also providing an in-depth analysis of the function of this unique miRNA in tumor development and its interactions with anticancer therapies.

MicroRNAs

MicroRNAs, small non-coding RNA molecules, typically possess an approximate length of 22 nucleotides and function as crucial post-transcriptional modulators that perform a significant role in the regulation of gene expression. These microRNAs, commonly called miRNAs, exert their regulatory influence over gene expression by binding to their corresponding target mRNAs in a highly specific and sequence-dependent manner, thereby modulating the stability and translational efficiency of these messenger RNAs[5]. The canonical biogenesis pathway that governs the maturation of miRNAs is comprised of two primary stages: (i) the initial transcriptional activity leading to the generation of miRNA precursors within the confines of the nucleus and (ii) the subsequent translocation and intricate processing of these precursors in the cytoplasmic environment[6–8]. It is noteworthy that miRNA genes are strategically located within the genomic architecture's intronic and exonic regions, as referenced in various studies. Moreover, the loci of certain miRNAs are often found to be spatially adjacent to one another, as exemplified by the miR-17-92 cluster, which is typically co-transcribed, thereby functioning synergistically to regulate gene expression in a coordinated manner. The transcriptional process that governs the synthesis of miRNAs is intricately modulated by a diverse array of transcription factors and is executed by RNA polymerase II, resulting in the production of primary miRNAs (pri-miRNAs) that are characterized by a distinct stem-loop configuration and often exceed 1 kilobase in length[8]. Following their transcription, extensive pri-miRNAs undergo a series of sophisticated processing steps, culminating in the formation of hairpin-shaped precursor miRNAs (pre-miRNAs) that typically measure around 60 nucleotides in length. Within the cytoplasmic milieu, pre-

miRNAs are subjected to additional cleavage by a specific RNase III-like endonuclease known as Dicer, which facilitates the generation of mature miRNA duplexes [6].

miR-223-3p

The transcriptional activity of miRNAs is influenced by a multitude of transcription factors and is carried out by RNA polymerase II, resulting in primary miRNAs (pri-miRNAs) characterized by a stem-loop structure exceeding 1 kb in length. Following transcription, extensive pri-miRNAs undergo further processing, giving rise to 60-nucleotide hairpin-shaped precursor miRNAs (pre-miRNAs). In the cytoplasm, pre-miRNAs are subjected to additional cleavage by another RNase III-like endonuclease, Dicer, leading to the formation of mature miRNA duplexes[9]. These duplexes consist of the miRNA-5p strands derived from miR-223-3p (thereafter referred to as miR-223), along with miR-223-5p, which represents the mature miRNA product of the MIR223 gene, located on chromosome Xq12. The initially described and most well-known function of miR-223 is its role in the modulation of hematopoietic lineage differentiation. Additionally, it plays a critical role in regulating human embryonic stem cell and osteoclast differentiation[10].

MiR-223 is integral to the differentiation and activation of immune system cells. This function, along with its role in inflammatory processes, is closely associated with the initiation of cancer. MiR-223 influences innate immunity through critical regulation of the maturation, differentiation, and polarization of various immune cell types, including neutrophils, monocytes, and dendritic cells. Although miR-223 is absent in B and T lymphocytes, it is predominantly expressed in CD34neg hematopoietic cells within the bone marrow, particularly in mature granulocytes, indicating a potential correlation between the expression of miR-223 and this specific differentiation pathway[11].

Vian and colleagues confirmed that the overexpression of miR-223 is related with enhanced granulopoiesis and concurrently inhibits erythropoiesis[12]. These findings partially contradict the results reported by Johnnidis and collaborators, who discovered that miR-223 negatively regulates granulopoiesis [13]. Furthermore, granulocytes lacking miR-223 were hyperactive—they were “premature, hypersensitive to activating stimuli, and exhibited increased fungicidal activity”—resulting in miR-223 mutant mice experiencing spontaneous lung inflammation and excessive tissue damage in response to endotoxin challenge[6,12].

MiR-223 significantly influences the functions of immune cells by targeting the mRNAs associated with the cellular stress sensors, notably NLRP3, within murine neutrophils and macrophages[14]. Research conducted by Feng and colleagues confirmed that miR-223 shows a pivotal role in inhibiting the NLRP3 inflammasome's activity, thereby mitigating acute lung injury/acute respiratory distress syndrome (ALI/ARDS). Furthermore, miR-223 reduces the formation of neutrophil extracellular traps (NETs) generated by granulocytes. Elevated levels of miR-223 in neutrophils impede mitochondrial reactive oxygen species (ROS) generation by obstructing Ca^{2+} influx, which subsequently inhibits interleukin (IL)-18-driven NET formation[15]. The heightened presence of exosomal miR-223 derived from neutrophils attenuates NLRP3 inflammasome assembly by reducing IL-18 synthesis in macrophages. In alignment with this, Ye and colleagues indicated that in a murine model of acute liver failure (ALF), a deficiency in miR-223 leads to an increase in vivo production of neutrophil elastase (NE), thereby promoting NET formation [16].

Glioma and Glioblastoma

Malignant gliomas and glioblastoma (GBM) represent the greatest prevalent neoplasms of the CNS, accounting for over 80% of all CNS tumors. Between these cancers, GBM is not only the most prevalent but also the most deadly, with a median survival time of just 15 months after diagnosis, despite the introduction of the Stupp protocol-based aggressive treatment in 2005. The recent World Health Organization (WHO) classification of CNS tumors in 2021 has delineated GBM as distinct from gliomas; thus, from both a histopathological and molecular perspective, GBM constitutes its legitimate entity. Conversely, gliomas can be stratified into low-grade (grades I and II; characterized by slow proliferation and generally favorable prognoses) and

high-grade (grade III; marked by rapid growth and infiltration, typically associated with poor prognoses). Although advancements in understanding the molecular underpinnings of gliomas and GBM have been made, there remains a dearth of biomarkers that serve as reliable diagnostic, prognostic, or therapeutic indicators[16–18].

GBM represents the furthermost prevalent form of incurable brain tumor among adults. Annually, the United States reports over 22,000 new cases of GBM. The current standard treatment modalities for GBM include surgical resection, radiotherapy, and chemotherapy, either individually or in combination; however, these interventions typically extend survival by only a few months. To enhance therapeutic outcomes, adjuvant strategies such as targeting angiogenesis and bolstering tumor immunity are employed alongside conventional treatments. A comprehensive understanding of the brain tumor microenvironment is crucial for improving the efficacy of GBM therapies. Recent investigations have concentrated on the GBM microenvironment, revealing abnormal activation of inflammasomes in human cases[19]. Inflammasomes serve as molecular complexes that are activated in response to pathogen invasion or the processing of proinflammatory cytokines, including interleukin-1 beta (IL-1β) and interleukin-18 (IL-18). Caspases, a family of cysteine proteases, play a significant role in mediating inflammation and cell death, with caspase-1 being pivotal in the maturation of IL-1β and IL-18 during inflammatory responses. IL-1β is produced at sites of infection or injury. Research indicates that human glioblastoma cells are capable of synthesizing IL-1, which influences the glioblastoma microenvironment and promotes tumor migration and invasion. Additionally, the cytokine monocyte chemoattractant protein-1 (MCP-1/CCL_2) has been associated with enhanced tumor growth. Furthermore, the inhibition of CCL_2 has been shown to impede the proliferation of GBM cells[20]. The schematic of a healthy brain and a brain with GB is manifested in Figure 1.

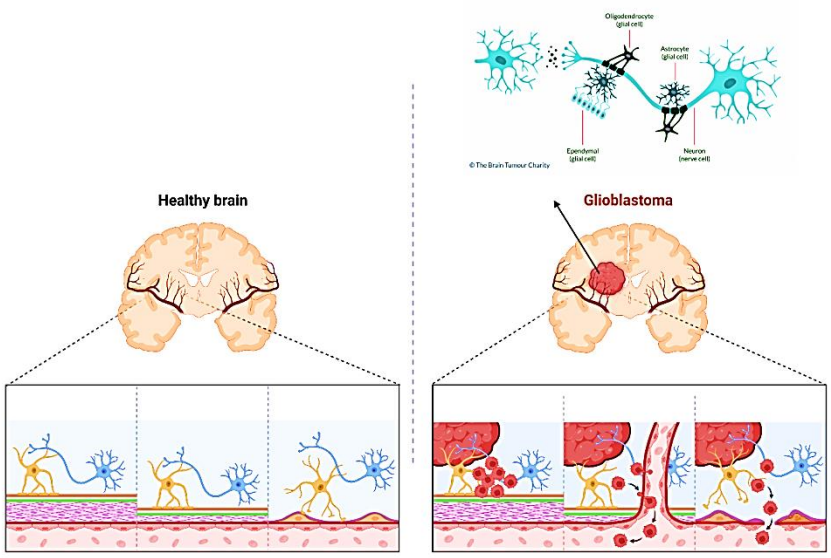

Figure 1. Malignant gliomas and glioblastoma and healthy brain.

Just like other tumors, the expression profiles of various microRNAs are modified in glioma and GBM cells associated to normal brain tissue. In many cases, the abnormal expression of these miRNAs corresponds with their functional roles, which include changes in target expression and effects on neoplastic traits. Recently, the significance of additional non-coding RNAs, such as long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs), in influencing miRNA-driven gene expression has been recognized [21].

MiR-223 as an Onco-Suppressor

Glasgow and associates were pioneers in postulating that miR-223 functions as an onco-suppressor in CNS tumors, predominantly in GBM, through investigations conducted during chicken embryogenesis. Moreover, the expression levels of miR-223 and NFIA exhibit an inverse correlation in human GBM biopsy specimens (Figure 2)[22]. Additionally, the GBM cell line U87, which ectopically overexpresses miR-223, demonstrates significantly reduced proliferation compared to control cell lines, attributable to G1 phase cell cycle arrest induced by the activation of the p21 onco-suppressor[23].

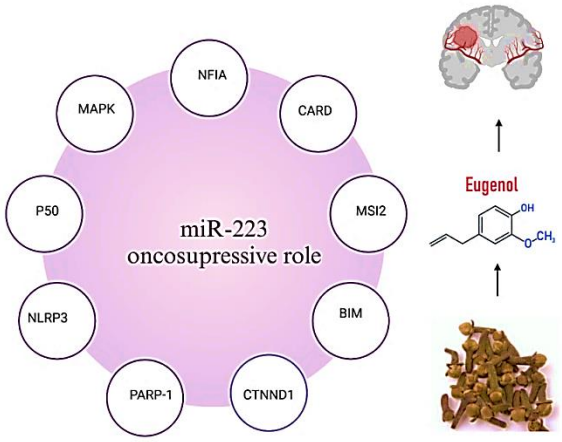

Figure 2. The Onco-suppressive role and molecular effects on miR-223-3p.

In a study involving GBM biopsies and cellular models, Ding et al. illustrated that miR-223 serves as an onco-suppressor by attenuating cell proliferation and migration through the downregulation of its direct target, NLRP3, which is implicated in inflammasome formation. This downregulation consequently leads to a reduction in NLRP3-associated pro-inflammatory cytokines as well as the pro-inflammatory mediator caspase 1[20].

Sequentially, the functionality of miR-223 is modulated by at least two upstream long non-coding RNAs (lncRNAs), namely SNHG29 and PITPNA-AS-1, both of which exhibit upregulation in GBM. Han et al. elucidated that SNHG29, through a competing endogenous RNA (ceRNA) mechanism, functions as a molecular sponge for miR-223[24]. Consequently, this interaction facilitates the activation of delta 1 catenin (CTNND1), a direct target of miR-223, thereby promoting enhanced cellular proliferation and migration via the Wnt/β-catenin signaling pathway. Geng et al. established that the tumor-suppressive function of miR-223 is impeded by PITPNA-AS-1 within GBM cells [25].

Zhang et al. established a positive association between miR-223 expression and the expression of genes related to epithelial-mesenchymal transition (EMT). Additionally, the forced expression of miR-223 in GBM cell lines was found to augment their invasive properties[26]. Similarly, Huang et al. perceived that several GBM cell lines exhibited elevated levels of miR-223 associated with the human fetal glial cell line HFGC. They also reported a significant reduction in the expression of its tumor-suppressive target, paired box 6 (PAX6); GBM tissues showed increased miR-223 levels alongside decreased PAX6 expression when compared to control tissues, as demonstrated through immunohistochemical analysis on a tissue microarray [27].

MiR-223 as a biomarker

The tumor-suppressive role of miR-223 has been substantiated by a multitude of studies indicating a favorable relationship between its expression levels and survival rates in patients with GBM. Wang et al. recognized miR-223 as part of a cluster of five microRNAs whose expression in tissue samples is related to improved overall survival in glioma and GBM patients. These microRNAs target shared

pathways that promote processes such as neuronal migration, responses to transforming growth factors, and pro-survival signaling pathways, including MAPK signaling[2].

In a similar context, Li et al. characterized miR-223 as a defensive microRNA specifically within the mesenchymal subtype of GBM. Conversely, Huang et al. found that increased levels of miR-223, along with a gene expression profile derived from cancerous tissues consisting of 16 mediator protein-coding genes, act as negative prognostic factors in GBM[28]. Importantly, Lu et al. identified miR-223, along with five other microRNAs, as a prognostic marker in low-grade gliomas, while noting that its elevated expression in GBM tissues was associated with an increased risk. Supporting Lu et al.'s findings, elevated concentrations of miR-223 were observed in pre-operative blood samples from patients with diffuse low-grade glioma compared to healthy individuals. Additionally, Roth et al. reported higher levels of miR-223 in blood samples from GBM patients in comparison to healthy controls [29].

'miR-223' constitutes a 9-microRNA cluster pinpointed in glioma case studies, showing tumor size variations tied in sync with volume fluctuations in less malignant gliomas (LGG) and high-grade tumors (GBM), suggesting it is a monitoring tool for disease progression [30].

In the study led by Renindra, Ananda, and Aman in 2024, the upsurge in circulating microRNA-223 signaling was noticeably more prevalent in aggressive brain tumors, indicating its significant utility for differentiating glioma individuals from those without the condition. The expression levels of this factor are linked to certain mechanisms responsible for the development of tumors, shedding light on its crucial role in diagnosing and predicting the outcomes for patients with gliomas[31]. Further, the examination of miR-223 took place among 107 patients with cerebral tumors above the tentorium, suggesting its potential as a tool for predicting tumor properties and outlooks for survival, consequently improving forecast reliability for these cancer patients. MicroRNAs are identified as biomarkers for glioma malignancy diagnosis. The prognostic significance of microRNAs for patient survival was established[32].

The Role of MiR-223 in drug resistance and prognosis

Huang et al. identified a significant association between increased levels of miR-223 and the chemoresistance observed in glioma stem cells (GSCs) when exposed to temozolomide (TMZ). This resistance was linked to a decrease in PAX6 expression, which subsequently activates the PI3K/AKT signaling pathway[33]. In a related study, Cheng et al. established that the suppression of miR-223 results in reduced chemoresistance of glioblastoma (GBM) cells to TMZ treatment[34]. Supporting the tumor-suppressive function of miR-223 in GBM, Liang et al. found that the overexpression of miR-223 increases the sensitivity of the U87 GBM cell line to radiation-induced apoptosis. Their results indicated that the reduction in tumor volume following radiotherapy in xenograft models with U87 cells overexpressing miR-223 was considerably more pronounced than in control xenograft models[35]. Mekala et al. illustrated that N-acetyl L-aspartate and Triacetin, two compounds with oncosuppressive effects, enhance the expression of various oncosuppressive microRNAs, including miR-223, thereby improving the chemosensitivity of GBM cells and inducing apoptosis[36].

Eugenol

Clove (*Syzygium aromaticum* (L.) of the Myrtaceae family) is regarded as a noteworthy herb in traditional medicine, exhibiting a wide range of biological activities. The phytochemical composition of clove includes various classes and groups of chemical compounds, such as hydrocarbons, monoterpenes, phenolics, and sesquiterpenes [37]. Among these active constituents, eugenol is noted for its numerous biological properties, including antioxidant, anticarcinogenic, antibacterial, and insecticidal effects. In addition to its common use as a flavoring agent in food, clove oil has historically been employed as a topical analgesic in dental practices[4]. Eugenol, a phenolic aromatic compound primarily sourced from clove oil, was first identified as an aromatic substance from Eugenia

caryophyllata in 1929 and became commercially available in the United States in 1940. Due to its diverse characteristics, eugenol has numerous applications and is considered a potential ingredient in various therapeutic products aimed at treating human cancers, reflecting the growing interest in traditional medicines that incorporate natural components[37–39]. Additionally, isoeugenol derivatives have emerged as a prominent area of research due to their beneficial properties, including antimicrobial activities. Consequently, eugenol has been extensively studied for its various effects, such as anti-inflammatory and antioxidant properties [40]. Numerous studies have revealed different molecular pathways associated with the therapeutic mechanisms of eugenol in the treatment of various cancers. Eugenol is classified as an aromatic compound within the phenolic group. It is the primary component of clove oil and is typically extracted from the essential oils of various plant families, including Myrtaceae, Lauraceae, Lamiaceae, and Myristicaceae. While the presence of eugenol can vary among different species, *S. aromaticum* is recognized as the most abundant source, with concentrations ranging from 9.38 to 14.65 g per 100 g of fresh plant material, contributing significantly to its characteristic fragrance[38,40].

Recent literature indicates that eugenol demonstrates anticancer properties through various interconnected mechanisms, thereby addressing the hallmark characteristics of excessive cellular growth. The proposed mechanisms include the induction of apoptosis, cell cycle arrest, inhibition of angiogenesis, and the dual roles of acting as both an oxidant and a pro-oxidant[41,42]. Additionally, eugenol is noted for its ability to inhibit inflammation and prevent cellular invasion and metastasis. Some studies have also highlighted the roles of autophagy and necroptosis. The specific mechanisms at play can differ based on the cancer type, dosage, and temporal factors. Furthermore, research has indicated that eugenol may have a chemopreventive effect when used in conjunction with other cytotoxic agents[43].

Eugenol on Glioblastoma

Eugenol exhibits antitumor effects linked to the induction of apoptosis across various cancer cell types. Research indicates that eugenol triggers apoptosis in RBL-2H3 mast cells and HL-60 human promyelocytic leukemia cells. Additionally, eugenol shows promise as a therapeutic adjunct in treating neuropathy within rat brain models. Nevertheless, the impact of eugenol on human glioma cells remains ambiguous. GBM represents the most aggressive and common form of malignant gliomas found in the human brain. The apoptosis of GBM cells plays a significant role in neuroprotection within the human brain. Therefore, it is essential to further investigate the apoptotic pathways in GBM cells[44].

Eugenol has been demonstrated through numerous studies to inhibit the cell cycle in numerous cancer cell lines, a finding that underscores its significance in anti-tumor activity. This inhibition occurs at distinct phases, specifically G1/S or G2/M, and is regulated by an intricate network of cell cycle proteins, including cyclins and cyclin-dependent kinases (CDKs)[45]. The research conducted by Owa et al. brought to light the critical role of genes in G1 phase regulation and pointed out the persistent initiatives to develop innovative chemotherapeutic agents that specifically target this phase, including flavopiridol, recognized for its efficacy as an inhibitor of cyclin-dependent kinases[46].

Wei-Zhe Liang et al, in 2015, investigated the effects of eugenol on intracellular free calcium levels ($[Ca^{2+}]i$) and its role in inducing apoptosis in DBTRG-05MG human glioblastoma cells. The results demonstrated that eugenol led to an increase in $[Ca^{2+}]i$, which was mitigated by the removal of extracellular calcium. Furthermore, eugenol was found to induce apoptosis by enhancing the production of ROS, diminishing mitochondrial membrane potential, releasing cytochrome c, and activating caspase-9 and caspase-3. Collectively, these findings suggest that in DBTRG-05MG cells, eugenol triggers increases in $[Ca^{2+}]i$ through a phospholipase C-dependent mechanism that releases calcium from the endoplasmic reticulum, while also facilitating calcium influx, potentially via TRPM8 or PKC-sensitive channels[47].

The compound eugenol is recognized for its potent antioxidant capabilities, which facilitate the scavenging of

free radicals and subsequently reduce oxidative stress, an important element in the processes of carcinogenesis and tumor promotion. Bezerra et al. have indicated that eugenol can exhibit a dual influence on oxidative stress, serving as an antioxidant in some contexts while acting as a pro-oxidant in others, depending on cellular conditions[48].

Eugenol has confirmed the capability to inhibit both the expression and activity of COX-2, thus contributing to its anti-inflammatory and anti-cancer effects. [49]. The dual targeting of COX-2 pathways by eugenol proposes its potential as an alternative to NSAIDs for the management of several diseases[43,50].

The role of VEGF is pivotal in angiogenesis, as it encourages the proliferation and survival of endothelial cells. Evidence from various cancer models suggests that eugenol may inhibit VEGF signaling. Specifically, in a rat model of malignant gastric carcinoma induced by N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), eugenol was observed to downregulate the expression of VEGF and VEGFR2. This downregulation was associated with a reduction in microvessel density and a decrease in tumor growth[51]. Research has shown that eugenol significantly diminishes the levels and function of MMPs in various cancer models. Specifically, eugenol treatment has been found to block both the function and production of MMP-9, a crucial enzyme that plays a role in breaking down the extracellular matrix (ECM) and the movement of human fibrosarcoma cells[52,53].

Various studies across diverse cancer models have demonstrated how eugenol mediates the modulation of this pathway. The belongings of eugenol and its derivatives, including eugenolol and glyceryl-isoeugenol, have been shown to suppress LPS-induced iNOS expression in macrophages. This suppression is facilitated by a decrease in NF-κB and AP-1 activity, which results from the inhibition of MAPK signaling pathways and the degradation of AKT/IκBα[50].

So, the compound eugenol exerts its effects on a broad spectrum of proteins and genes that are implicated in the progression of cancer. It downregulates the expression of important transcription factors, namely c-Myc, E2F1, and H-ras, which are essential for cell growth and longevity. Furthermore, eugenol promotes the upregulation of genes related to apoptosis, including Bcl-2, Bax, and survivin, thereby facilitating the programmed death of malignant cells[54].

Zhenjiang, Li et al., 2020 showed that Eugenol-entrapped chitosan polymer exhibit critical physical and functional attributes of a copolymer suitable for drug application. Findings from immunocytochemical investigations reveal a reduction in NFκβ protein expression, while flow cytometry corroborates apoptosis induction by EuCs [54].

Eugenol has been observed to exert a defensive mechanism whereby it reduces the expression levels of phosphate-Akt and MMP-2 in lung carcinoma cells[54]. In breast carcinoma cell lines, the extract derived from *Annona muricata* demonstrated superior anti-cancer efficacy. Numerous phytochemicals are acknowledged for their potential anti-cancer, anti-inflammatory, and antioxidant properties. Compounds sourced from plants are documented to improve the bioavailability of pharmaceuticals within the intestinal tract, which is essential in impeding the proliferation of malignant cells. Certain phytopigments serve as natural agents in cancer prevention and enhance the targeted delivery of therapeutic agents to neoplastic sites[55].

Based on previous studies, eugenol-encapsulated nanoemulsions facilitate apoptotic processes; consequently, both cell cycle dynamics and apoptosis were analyzed utilizing flow cytometry. Hepatic cells and colonic cells demonstrate an elevated percentage of apoptosis when subjected to treatment with eugenol and canola oil formulations. The pervasive presence of eugenol exerts an opposing effect on colon carcinoma cells by promoting apoptosis in HCT-15 and HCT-29 lines. This phenomenon can be ascertained through the assessment of MMP and the sequential generation of ROS in neoplastic cells following a specified duration of treatment[56].

miR-223-3p is recognized for its regulatory role in inflammation and apoptosis through the targeting of proteins such as NLRP3, an integral part of the inflammasome implicated in inflammatory responses. In the scenario of high glucose-induced apoptosis within endothelial cells, miR-223-3p has been demonstrated to confer protective effects by down-regulating NLRP3 and pro-apoptotic

proteins, thereby indicating its significance in promoting cell survival. The anesthetic propofol has been observed to enhance the expression of miR-223-3p, which subsequently mitigates inflammation and cognitive impairments in aged rats[1,57]. This finding suggests that specific compounds may modulate miR-223-3p expression and its consequential effects. In oncological contexts, miR-223-3p may function as either an oncogene or a tumor suppressor, contingent upon the specific circumstances, with its expression being influenced by various elements, including other microRNAs and transcription factors. Although the direct impact of eugenol on miR-223-3p is not explicitly documented in the referenced studies, its established anti-inflammatory and antioxidant characteristics imply a potential capability for modulating pathways associated with miR-223-3p, akin to other compounds such as propofol. Additional investigations are warranted to elucidate eugenol's specific effects on miR-223-3p expression and its prospective therapeutic applications in scenarios where miR-223-3p is critical.

CONCLUSIONS

The study concludes that miR-223 is a critical controller of gene expression and shows an important role in numerous biological processes, including hematopoietic lineage differentiation, immune system regulation, and cancer development.

The conclusions of the study propose that miR-223 may be a valuable biomarker for glioma diagnosis and prognosis, and that eugenol may be a potential therapeutic agent for the treatment of gliomas. Eugenol may have potential therapeutic applications in scenarios where miR-223-3p is critical, although further investigations are needed to elucidate its specific effects on miR-223-3p expression. Future studies can focus on further elucidating the molecular mechanisms underlying the role of miR-223 in regulating gene expression and its implications in various biological processes. Future work may involve further investigation of the mechanisms of miR-223 and eugenol in glioma diagnosis and treatment, as well as the improvement of therapeutic strategies that target these molecules. Further investigations are needed to elucidate eugenol's specific effects on miR-223-3p expression and its prospective therapeutic applications.

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Conflict of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence this paper.

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