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MINIREVIEWS

Britanin – a beacon of hope against gastrointestinal tumors?

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Abstract

Britanin is a bioactive sesquiterpene lactone known for its potent anti-inflammatory and anti-oxidant properties. It also exhibits significant anti-tumor activity, suppressing tumor growth *in vitro* and *in vivo*. The current body of research on Britanin includes thirty papers predominantly related to neoplasms, the majority of which are gastrointestinal tumors that have not been summarized before. To drive academic debate, the present paper reviews the available research on Britanin in gastrointestinal tumors. It also outlines novel research directions using data not directly concerned with the digestive system, but which could be adopted in future gastrointestinal research. Britanin was found to counteract liver, colorectal, pancreatic, and gastric tumors, by regulating proliferation, apoptosis, autophagy, immune response, migration, and angiogenesis. As confirmed in pancreatic, gastric, and liver cancer, its most commonly noted molecular effects include nuclear factor kappa B and B-cell lymphoma 2 downregulation, as well as Bcl-2-associated X protein upregulation. Moreover, it has been found to induce the Akt kinase and Forkhead box O1 axis, activate the AMP-activated protein kinase pathway, elevate interleukin-2 and peroxisome proliferator-activated receptor-γ levels, reduce interleukin-10, as well as downregulate matrix metalloproteinase-9, Twist family bHLH transcription factor 1, and cyclooxygenase-2. It

also inhibits Myc–HIF1α interaction and programmed death ligand 1 transcription by interrupting the Ras/RAF/MEK/ERK pathway and mTOR/P70S6K/4EBP1 signaling. Future research should aim to unravel the link between Britanin and acetylcholinesterase, mast cells, osteolysis, and ischemia, as compelling data have been provided by studies outside the gastrointestinal context. Since the cytotoxicity of Britanin on noncancerous cells is significantly lower than that on tumor cells, while still being effective against the latter, further in-depth studies with the use of animal models are merited. The compound exhibits pleiotropic biological activity and offers considerable promise as an anti-cancer agent, which may address the current paucity of treatment options and high mortality rate among patients with gastrointestinal tumors.

Key Words: Britanin; Sesquiterpene lactones; Chemotherapeutics; Gastrointestinal tumors; *In vitro*; *In vivo*

Core Tip: Natural compounds have settled in the development of novel drugs. Britanin is a sesquiterpene lactone whose effect on gastrointestinal tumors has not been summarized before. Our paper reviews the current state of knowledge and proposes novel research directions. Britanin was found to counteract liver, colorectal, pancreatic, and gastric tumors *via* the regulation of proliferation, apoptosis, autophagy, immune response, migration, and angiogenesis. Future research should examine the link between Britanin and acetylcholinesterase, mast cells, osteolysis, and ischemia. The compound holds promise as an anti-cancer agent and may overcome the paucity of treatment options or high mortality rate in gastrointestinal tumors.

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INTRODUCTION

Natural compounds have long been established in the development of novel drugs. One such group, the sesquiterpene lactones, are organic terpenoids that exhibit a broad spectrum of biological activities, with their anti-cancer, anti-parasitic, and anti-inflammatory properties being the most prominent[1-3]. One of the representatives of this group is a compound termed Britanin (C19H26O7), a pseudoguaianolide-type sesquiterpene lactone present in various Inula species. It has been found to demonstrate anti-cancer agent activities by affecting tumor cell survival[3,4]. Although Britanin has been present in the PubChem database since 2005, the current body of research is limited to about thirty papers in total, mostly related to cancer. The vast majority of the literature concerns gastrointestinal tumors that have not been summarized before. Britanin has also been evaluated in leukemia[5-8] and tumors of the breast[9-12], head and neck[13], kidney[14], prostate[15], or lung[14]; however, insufficient data exists on each disease type to draw firm conclusions. Given its promising implications in oncology, Britanin is likely to be the subject of considerable research in the upcoming years. To drive academic debate, the present paper reviews and discusses available research on Britanin in gastrointestinal tumors. A literature search was performed *via* PubMed using the "britanin" and "britannin" terms, focusing on gastrointestinal tumors. Moreover, the present paper outlines novel research directions using data outside the scope of the digestive system, which could be adopted in future gastrointestinal research.

RESEARCH ON BRITANIN IS FOCUSED ON LIVER, COLORECTAL, PANCREATIC, AND GASTRIC TUMORS

The first report on the anti-proliferative properties of Britanin was published in 2012 by Moghadam *et al*[14] who extracted a compound from Inula aucheriana. A strong cytotoxic effect was noted on the liver cancer cell line HepG2 based on MTT assay, *i.e.*, utilizing 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, with the half-maximal inhibitory concentration (IC_{50}) of 2.2 μg/mL[14]. In the following year, Fischedick *et al*[16] found that 10 μmol/L of Inula britannica-derived Britanin inhibited cell growth by ~80%, as estimated on colorectal cancer cell line DLD1 and its multidrug resistant counterpart with P-glycoprotein overexpression.

In 2016, Piao *et al*[17] evaluated the activity of fourteen Inula japonica-derived compounds that inhibit DNA topoisomerases. Among them, Britanin exhibited better inhibitory activity against topoisomerase II (IC_{50} = 6.9 μmol/L) than against topoisomerase I (IC_{50} > 80 μmol/L). Interestingly, the inhibitory capabilities of Britanin directed at topoisomerase II were found to surpass those of Etoposide (IC_{50} = 26.9 μmol/L), a commonly used inhibitor. Moreover, Britanin showed low toxicity against liver hepatoblastoma (HepG2 cell line) and colon adenocarcinoma (HT-29 cell line), with IC_{50} values

of 35.5 μmol/L and 3.9 μmol/L, respectively[17].

In 2017, Moeinifard *et al*[18] assessed the chemotherapeutic potential of Britanin derived from Inula aucheriana in pancreatic cancer therapy. The results indicated that the compound induces apoptosis in human pancreatic cancer cell lines AsPC-1 and PANC-1 by simultaneously decreasing B-cell lymphoma 2 (BCL-2) expression and increasing that of Bcl-2-associated X protein (BAX). Additionally, Britanin increased the generation of reactive oxygen species (ROS) and activated the axis of Akt kinase and Forkhead box O1 (AKT-FOXO1), inducing the mitochondrial apoptotic pathway in both cell lines[18]. IC_{50} values for AsPC-1 and PANC-1 cell lines equaled 30 ± 4.61 μmol/L and 40 ± 5.63 μmol/L, respectively.

In the following year, Cui *et al*[19] reported that Britanin extracted from Inula aucheriana could induce apoptosis and autophagy *via* ROS-driven activation of the AMP-activated protein kinase (AMPK) pathway in the liver cancer cell lines HuH-7, SMMC-7721, and HepG2. Britanin reduced the survival rate of the cells in a dose- and time-dependent manner, with respective IC_{50} values of 27.86 ± 1.35 μmol/L, 28.92 ± 1.09 μmol/L and 15.69 ± 1.58 μmol/L after 24-h treatment (8.81 ± 0.95 μmol/L, 8.12 ± 1.15 μmol/L, and 6.86 ±1.05 μmol/L after 48 h). Furthermore, the compound exhibited no cytotoxicity against normal human liver cells. Further *in vivo* tests on the most susceptible cell line (HepG2) found Britanin to suppress liver cancer proliferation in a dose-dependent manner[19].

In 2020, Shi *et al*[20] found Inula japonica-derived Britanin to inhibit the growth and progression of gastric cancer cells using *in vitro* and *in vivo* models. The *in vitro* study examined the influence of Britanin on the proliferation and migration of BGC-832 and SGC-7901 gastric cell lines, while the mouse xenograft model involving the BGC-823 allowed for real-time tracking of tumor growth through bioluminescent imaging. Cytotoxicity testing indicated IC_{50} values of 4.999 μmol/L for BGC-823 and 2.243 μmol/L for SGC-7901. Treatment with Britanin was associated with alterations in the nuclear factor kappa B (NF-κB) pathway which reduced the proliferation of gastric cancer cells. It also resulted in elevated interleukin-2 levels (activator of Natural Killer cells, B-cells, CD4+ and CD8+ T-cells) and decreased interleukin-10 levels (CD4+ T-cell inactivator), thus promoting the immune response and inhibiting cancer cell development[20].

A study by Li *et al*[21] found Britanin to have similar effects on hepatocellular carcinoma. The cytotoxicity and anti-tumor effects were studied on HepG2 and BEL-7402 cell lines *in vitro* and a subcutaneous BEL-7402 tumor model in mice *in vivo*. The IC_{50} values were found to be 2.702 μmol/L in the BEL-7402 and 6.006 μmol/L in the HepG2 cells. Colony formation assay, transwell migration, and tumor size measurements showed that Britanin possesses a reliable anti-tumor effect. Additionally, Western Blotting indicated that Britanin inhibited p65 protein and modulated the BCL-2/BAX ratio [21].

The effect of Britanin from Inula linearifolia on pancreatic cancer was examined by Li *et al*[22]. The anti-tumor effects were determined *in vitro* on three pancreatic cancer cell lines: PANC-1, MIA CaPa-2, and BxPC-3. Respective IC_{50} values equaled 1.348, 3.104, and 3.367 μmol/L. PANC-1 was utilized to establish a murine xenograft model. Britanin exhibited very low toxicity *in vivo* and excellent inhibitory effects against pancreatic cancer *in vivo* and *in vitro*. The compound diminished cell proliferation and migration by inhibiting the p50-p65/NF-κB pathway. The authors suggest that, due to its very low toxicity, Britanin could be safer for use than small molecule inhibitors[22].

In 2021, Zhang *et al*[23] investigated the potential of Britanin in cancer immunotherapy, specifically its impact on the Programmed death receptor 1 and ligand 1 (PD-1/PD-L1) immune pathway. The study used Hep3B liver cancer cells and HCT116 colorectal cancer cells, with the latter utilized to establish a mouse xenograft model. It was found that Britanin maintains the activity of T-cells and reduces proliferation and angiogenesis by inhibiting PD-L1 transcription; this was achieved by interrupting the Ras/RAF/MEK/ERK pathway and mTOR/P70S6K/4EBP1 signaling, ultimately affecting communication between myelocytomatosis oncogene (Myc) and hypoxia-inducible factor 1α (HIF-1α). Moreover, molecular docking data revealed that Britanin interacts with PD-L1, HIF-1α, and Myc[23]. A later docking analysis of Britanin, and fifteen of its analogues, to the PD-L1 protein was used in the design of novel molecules based on the structure of pseudoguaianolide-type sesquiterpene lactones[4].

The most recent gastrointestinal study was conducted by Abdolmohammadi *et al*[24] who evaluated the mode of action of Britanin from Inula aucheriana in gastric cancer. Growth inhibition and apoptosis induction were noticed in AGS and MKN45 cell lines, where Britanin suppressed the NF-κB pathway by increasing the mRNA and protein levels of peroxisome proliferator-activated receptor-γ (PPARγ). Upregulation of BAX and downregulation of BCL-2, matrix metalloproteinase-9 (MMP-9), Twist family bHLH transcription factor 1 (TWIST-1), and cyclooxygenase-2 (COX-2) were also noted. The authors concluded that Britanin is an encouraging anti-cancer agent that still requires further examination [24].

The main biological and molecular findings from the above studies are briefly summarized in Figure 1, whereas available IC_{50} values are collected in Table 1. It is worth recapitulating a few aspects that make Britanin a promising anti-cancer agent. Above data certify that the compound exhibits pleiotropic biological activity, providing a multimodal approach against gastrointestinal tumors. Combining these properties with the impact of Britanin on the PD-1/PD-L1 pathway[4,23], it seems that the compound might be valuable for both chemotherapeutic and immunotherapeutic settings. Moreover, available studies report that the cytotoxic effect of Britanin on noncancerous cells is significantly lower than that on tumor cells, while still being effective against the latter[18,19,22]. Ultimately, it has been suggested that Britanin could be safer than small molecule inhibitors[22], which are currently used for targeting gastrointestinal tumors [25,26].

FUTURE PROSPECTS

A wealth of data on the effect of Britanin has been obtained from studies other than those associated with liver, colorectal, pancreatic, and gastric cancer. Such information may suggest the direction of further research on gastrointestinal tumors.

Table 1 Efficacy of Britanin from various plant sources in inhibiting gastrointestinal cancer cell lines

Gastrointestinal tumor	Cell line	Source of Britanin	IC_{50} (μmol/L)	Ref.
Liver cancer	HuH-7	*Inula aucheriana*	27.86 ± 1.35[3]	Cui *et al*[19]
Liver cancer	SMMC-7721	*Inula aucheriana*	28.92 ± 1.09[3]	Cui *et al*[19]
Liver cancer	HepG2	*Inula aucheriana*	15.69 ± 1.58[3]	Cui *et al*[19]
Liver cancer	HepG2	*Inula aucheriana*	6.004[1,4]	Moghadam *et al*[14]
Liver cancer	HepG2	*Inula japonica*	35.5[5]	Piao *et al*[17]
Liver cancer	HepG2	*Unspecified*[2]	6.006[5]	Li *et al*[21]
Liver cancer	BEL-7402	*Unspecified*[2]	2.702[5]	Li *et al*[21]
Colorectal cancer	HT-29	*Inula japonica*	3.9[5]	Piao *et al*[17]
Pancreatic cancer	MIA CaPa-2	*Inula linearifolia*	3.104[4]	Li *et al*[22]
Pancreatic cancer	BxPC-3	*Inula linearifolia*	3.367[4]	Li *et al*[22]
Pancreatic cancer	PANC-1	*Inula linearifolia*	1.348[4]	Li *et al*[22]
Pancreatic cancer	PANC-1	*Inula aucheriana*	40 ± 5.63[3]	Moeinifard *et al*[18]
Pancreatic cancer	AsPC-1	*Inula aucheriana*	30 ± 4.61[3]	Moeinifard *et al*[18]
Gastric cancer	BGC-832	*Inula japonica*	4.999[4]	Shi *et al*[20]
Gastric cancer	SGC-7901	*Inula japonica*	2.243[4]	Shi *et al*[20]

[1]Recalculated from μg/mL to μmol/L to standardize the unit (molecular weight of Britanin, *i.e.*, 366.4 g/mol, was acquired from PubChem 2.1).
[2]Unspecified Britanin source (non-open access paper with no data in abstract).
[3]24-h incubation time with Britanin.
[4]72-h incubation time with Britanin.
[5]Unspecified incubation time with Britanin (non-open access paper or no data).
IC_{50}: Half-maximal inhibitory concentration.

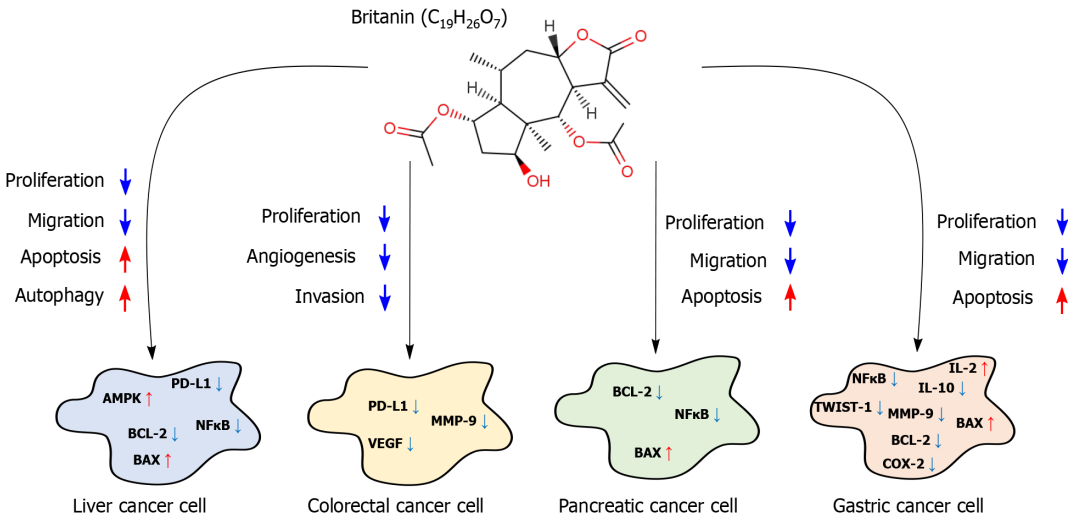

Figure 1 Influence of Britanin on biological processes and related proteins in gastrointestinal tumors. A red upward pointing arrow ("↑") indicates biological process activation by Britanin, whereas a blue downward pointing arrow ("↓") signifies biological process inhibition by the same compound. Similar applies to the level of proteins, the symbols of which are located in four multicolored areas representing liver, colorectal, pancreatic, and gastric cancer cells.

Firstly, Hajimehdipoor *et al*[27] discovered that three sesquiterpene lactones extracted from Inula aucheriana hold promise as inhibitors of acetylcholinesterase (AChE). While the research was primarily focused on Alzheimer's disease, Britanin emerged as the second most potent inhibitor of AChE, exhibiting 25.2% inhibitory activity at a concentration of 300 μg/mL. The researchers suggest that altering the structure of Britanin could enhance its AChE inhibitory potential and reduce its cytotoxicity[27]. This could be of value in cancer treatment, as the cholinergic system and AChE activity are known to play important roles in tumor development and microenvironmental alterations[28]. Modifying the structure of Britanin to reduce cytotoxicity is noteworthy since gastrointestinal toxicity remains a common complication

of cytotoxic anti-cancer chemotherapy[29].

Secondly, gastrointestinal research on Britanin should be directed at mast cells, which appear to play pro-tumorigenic and anti-tumorigenic roles[30]. Lu *et al*[31] assessed the anti-allergic activity of an Inula japonica extract *in vivo* and investigated its mode of action on mast cells *in vitro*. Britanin was found to be one of the most abundant sesquiterpenes. The extract attenuated the mast cell-mediated passive cutaneous anaphylaxis reaction and exhibited an anti-allergic effect by modulating eicosanoid generation and degranulation *in vitro*[31]. Park *et al*[32] found Inula japonica-derived Britanin to ameliorate mast cell-mediated pro-inflammatory responses, which they attributed to NF-κB activation. Similarly, Lu *et al*[33] found the mast cell-suppressing ability of Britanin to be associated with the inhibition of the spleen tyrosine kinase (Syk) pathway *via* Syk protein dephosphorylation, as well as deactivation of NF-κB and mitogen-activated protein kinases.

It has been observed that mast cell density appears to correlate with angiogenesis and progression in patients with gastric carcinoma[34]. Moreover, mast cells were found to be abundant in gastric cancer, which shorten patient survival [35]. The latter study also revealed that cancer-derived tumor necrosis factor alpha induces PD-L1 overexpression in mast cells *via* activation of the NF-κB signaling pathway. PD-L1+ mast cells suppressed T-cell growth and function in a PD-L1-dependent manner. Given that Britanin is associated with NF-κB, PD-L1, and T-cells, future gastrointestinal research should include Britanin and mast cells.

Thirdly, Britanin has been found to inhibit osteoclastogenesis and osteolysis. The compound inhibited osteoclast differentiation by downregulation of B lymphocyte-induced maturation protein 1 and nuclear factor of activated T cells 1 *in vitro*, as well as protected bone from titanium-induced calvarial osteolysis *in vivo*[36]. Although osteolysis is a complication among patients carrying titanium-based implants after long-term usage[37], it also occurs as an outcome of bone metastasis in colorectal cancer. The mechanism by which colorectal cancer cells influence the differentiation of bone marrow-derived monocytes into osteoclasts has been described previously[38]. However, further studies are needed to confirm whether Britanin can prevent metastasis of colorectal cancer while also counteracting the tumor itself.

Lastly, Britanin was found to relieve ischemic injury, a phenomenon characterized by tissue damage due to the lack of perfusion and oxygenation. Although a higher risk of hypoxia is typically associated with organ transplantation, the tumor microenvironment is similar to ischemic tissue in this regard[39]. Outside the gastrointestinal context, Britanin was found to ameliorate cerebral and myocardial ischemia *via* pathways incorporating the nuclear factor erythroid 2-related factor 2, which is one of the most important defenders against oxidative stress[40,41]. Thus, Britanin might be an important protector against negative outcomes of oxidative stress, to which rapidly dividing cells of colonic mucosa are steadily exposed[42]. Moreover, subsequent research on gastrointestinal tumors is necessary, since ischemia mediates metastasis in liver, pancreatic, and colon cancer[43-45].

The novel research directions which could be adopted in future gastrointestinal research on Britanin are recapitulated in Figure 2. Regardless of the topic, any studies of the relationship between Britanin and its influence on signaling pathways or the proteome should be supported by molecular docking. Existing data indicates that Britanin interacts with such essential proteins as NF-κB, PD-L1, Myc, and HIF-1α[4,12,23,46], and it may also influence other important proteins and pathways, such as BCL-2, BAX, AMPK, MMP-9, TWIST-1, COX-2, or PPARγ.

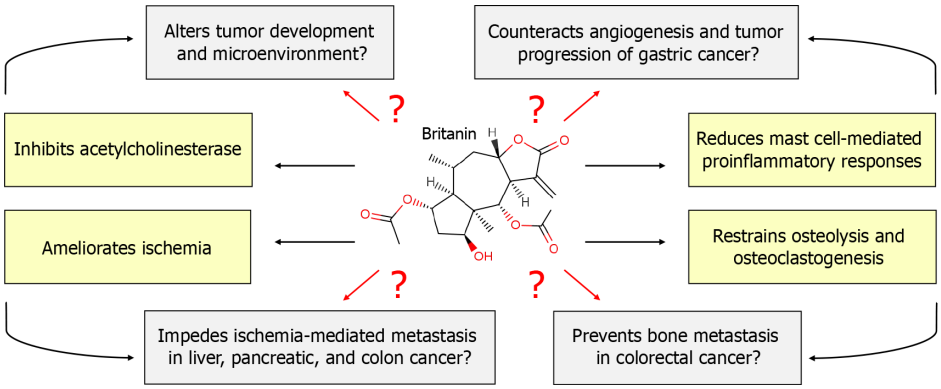

Figure 2 Novel research directions which could be adopted in future gastrointestinal research on Britanin. The light-yellow rectangles represent data on Britanin obtained from studies other than those associated with liver, colorectal, pancreatic, and gastric cancer. Processes included therein are linked to various tumor-related phenomena, which are depicted in gray rectangles. Britanin was not yet investigated in these tumor-related phenomena, which was marked with solid red arrows and question marks ("?"). Such information may suggest the direction of further research on gastrointestinal tumors.

CONCLUSION

Britanin is a natural compound that counteracts liver, colorectal, pancreatic, and gastric tumors by regulating proliferation, apoptosis, autophagy, immune response, migration, and angiogenesis. Its cytotoxicity on noncancerous cells is significantly lower than that on tumor cells, while still being effective against the latter, warranting further in-depth studies based on animal models. The ability to reduce the cytotoxicity of Britanin *via* structural modification may be useful in limiting gastrointestinal toxicity after cytotoxic anti-cancer chemotherapy. Outside the chemotherapeutic context, Britanin might also be valuable in an immunotherapeutic setting since it affects the PD-1/PD-L1 pathway. The

compound acts against negative outcomes of oxidative stress, to which rapidly dividing cells of colonic mucosa are steadily exposed. Given the pleiotropic biological activity, Britanin ensures a multimodal approach against gastrointestinal tumors, which may provide additional treatment options or reduce the high mortality rate. However, it has yet to be included in clinical trials as no data on its use exists in the National Institutes of Health. Future research should incorporate molecular docking simulations and focus on the link between Britanin and acetylcholinesterase, mast cells, osteolysis, and ischemia, as considerable data on its potential already exists outside the gastrointestinal context.

FOOTNOTES

Author contributions: Kajdanek A, Kołat D, and Kałuzińska-Kołat Ż conceptualized the article; Kałuzińska-Kołat Ż supervised the article; Kajdanek A, Kołat D, Zhao LY, Kciuk M, Pasieka Z, and Kałuzińska-Kołat Ż reviewed the literature; Kajdanek A wrote the original draft; Kajdanek A, Kołat D, Zhao LY, Kciuk M, Pasieka Z, and Kałuzińska-Kołat Ż reviewed and edited article; all authors have read and agreed to the published version of the manuscript.

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