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Echinomycin: A Journey of Challenges

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ABSTRACT

Echinomycin is a natural compound discovered and isolated from bacteria, introduced as a promising antibiotic and anticancer therapy. However, it failed clinically due to improper formulations and a short half-life. After the unsuccessful clinical trials, echinomycin was overlooked. Recently, a new mechanism of action has given some hope for reviving echinomycin as an inhibitor of hypoxia-inducible factor (HIF-1). In 2015, echinomycin received orphan drug designation for treating acute myeloid leukemia in the USA. Furthermore, advancements in drug delivery systems have provided new prospects to overcome the echinomycin formulation issues and explore further therapeutic benefits. This review details the echinomycin journey along with the main challenges of this potent drug and provides insights into possible future clinical applications.

Keywords: Echinomycin, targeted ligands, cyclic peptides, quinoxaline antibiotic, DNA bis-intercalator.

1. INTRODUCTION

Echinomycin (NSC526417) is a quinoxaline antibiotic peptide with a unique thioacetal bridge (2). It was initially isolated from Streptomyces echinatus bacteria in the 1950s and introduced as an antibiotic (3). It possesses potent antibacterial, anticancer, and antiviral activities. Echinomycin binds to double-strand DNA and intercalates into DNA at two specific sites, causing inhibition of DNA replication and RNA synthesis (4, 5). Echinomycin showed promise as a cytotoxic drug, leading to its progression to phase I and II clinical trials for various types of cancers (6). Research by Park et al. revealed that echinomycin is more effective against Staphylococcus aureus than vancomycin, both in vitro and in vivo in a mouse model. However, a major challenge in using echinomycin is its hydrophobic nature and water insolubility. Currently, echinomycin is under investigation for its antineoplastic effect as an inhibitor of hypoxia-inducible factor-1 (HIF-1), a critical factor in leukemia cell growth (7).

Furthermore, echinomycin has been observed to down-regulate numerous signaling pathways, including the Notch signaling pathway (3, 8). It is important to note that the most commonly reported toxicity associated with echinomycin is severe nausea and vomiting, a side effect that is comparable to other chemotherapeutic agents like actinomycin. To harness the full potential of this powerful drug, it is crucial to mitigate its toxicity and enhance its bioavailability and solubility (9). The objective of this current review is to comprehensively examine past and present research on echinomycin, shedding light on its potential future applications in clinical settings (10).

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2. ECHINOMYCIN DISCOVERY

Echinomycin was first discovered and isolated from Streptomyces echinatus species in Germany in 1957. Four years later, the same compound was produced by Streptomyces species in Japan and was given the name Quinomycin (11). Subsequently, more than thirty-seven members of the quinoxaline antibiotics were discovered (12). The identity of echinomycin (levomycin and quinomycin A) was conclusively determined in 1964. Quinomycin A was found to be identical to echinomycin based on paper chromatogram analysis of the compounds isolated from Streptomyces species (13).

A few years later, the mechanism of action of quinoxaline antibiotics was elucidated, revealing their interaction with deoxyribonucleic acid (DNA) (14). Waring and Wakelin described echinomycin's bifunctional intercalation activity with DNA (14). In 1975, the structure of echinomycin was reexamined and recharacterized using proton and carbon-13 nuclear magnetic resonance (NMR), electron impact, and field desorption mass spectrometry (15). Furthermore, through footprinting methods, a specific DNA binding site for echinomycin was identified as a 4-base pair sequence with the central two-base pair of 5'-CG-3' (16, 17).

Adams and Rinaldi conducted research on the effect of echinomycin on DNA methylation. They found that echinomycin does not inhibit DNA methylation, suggesting that methylation does not involve the transient separation of double strands. Instead, the primary effect of echinomycin was the inhibition of DNA and RNA synthesis (18).

Over the years, additional research and studies have been undertaken to further understand the potential of this highly potent drug. Echinomycin has been investigated for its antineoplastic effects, and its complete story, including its activity as an inhibitor of hypoxia-inducible factor 1 (HIF-1), has been newly developed (8, 19-21).

3. ECHINOMYCIN PROPERTIES

3.1. Physicochemical properties

Echinomycin is a hydrophobic, colorless, needle-like crystalline compound that is soluble in chloroform, dichloromethane, and dioxane but insoluble in water and hexane. Its distinction from other compounds was achieved using paper chromatography, where its retention factor (Rf) was determined to be 0.15 (22). In the early 1990s, the molecular model of echinomycin was defined through crystallographic data. Most color reactions with this compound are negative, except for the ninhydrin reaction in HCl at 100 °C. Echinomycin can be quantified in human plasma using High-Performance Liquid Chromatography (HPLC) (23, 24).

3.2. Echinomycin structure elucidation and biosynthesis

Echinomycin (NSC52641), also known as quinomycin A and levomycin, is a small molecule with a molecular weight of 1101.3 g/mol that belongs to cyclic depsipeptide antibiotics that have two quinoxaline moieties. It has a chemical name N, N'-(2,4,12,15,17,25-hexamethyl-11,24-bis(1-methylethyl)-27-(methylthio)-3,6,10,13, 16, 19, 23,26-octaoxo-9,22-dioxa-28-thia-2,5,12,15,18,25-hexaazabicyclo (12.12.3) nonacosane-7,20-diyl)bis (2-quinoxaline carboxamide) (13).

The precursors of the two quinoxaline rings are quinoxaline-2-carboxylic acid and 3-hydroxyquinaldic acid, as shown in Figure 1 (25). Additionally, the octapeptide backbone is a depsipeptide that is divided into two cycles via a thioacetal group (16). The thioacetal is a unique chemical group resulting from the disulfide bridge of triostin A, the precursor of echinomycin, through a methyltransferase and S-adenosyl-L-methionine-dependent pathway (26, 27). A depsipeptide is a peptide that contains one or more ester groups instead of amide groups, giving it both peptide and ester linkages. Echinomycin is a depsipeptide that contains two ester bonds connecting the two amino acids, valine and serine (28). The depsipeptide portion of echinomycin

(octapeptide dilactone) consists of two sets of four amino acids: alanine (L- methyl-Ala), cysteine (methyl -L- Cys), valine (L-Val), and serine (D-Ser), as illustrated in Figure 1 (17, 19). Echinomycin's structural features make it an extremely potent bifunctional DNA intercalator.

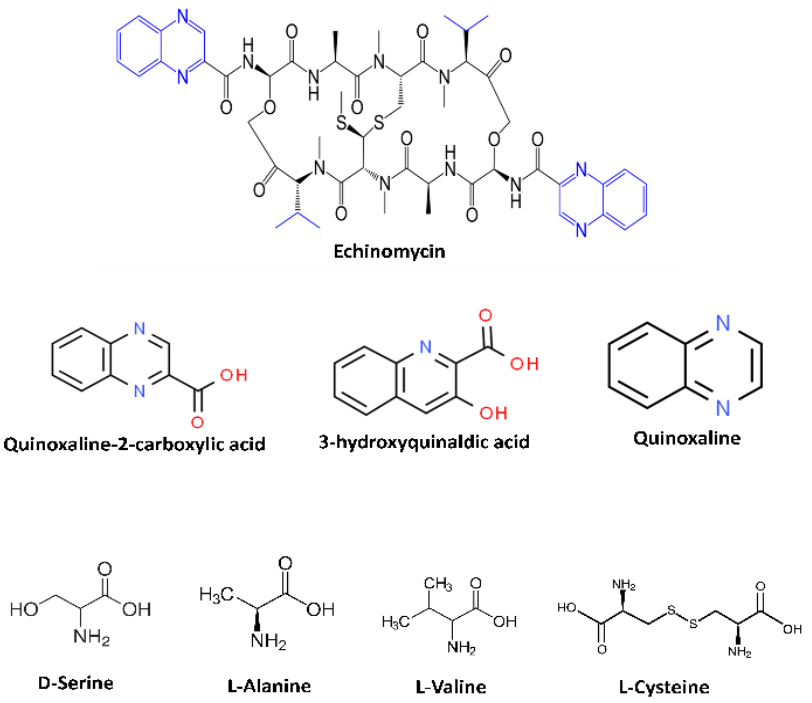

Figure 1: Echinomycin structure and components

Echinomycin is a secondary metabolite originally extracted and purified from Streptomyces echinatus bacteria (29, 30). The core structure of echinomycin is biosynthesized by the non-ribosomal peptide synthetase (NRPS) of this bacterium as part of its defense mechanism against other pathogens (27). The dimerized cyclic peptide core structure is attached to a bicyclic aromatic chromophore quinoxaline. Echinomycin has also been isolated from other bacteria, such as Streptomyces lasaliensis. Mass production of this valuable secondary metabolite for clinical use requires flexible and easily cultivated microorganisms for engineered biosynthesis. Therefore, biosynthesis of echinomycin in Escherichia coli was performed. Firstly, the gene cluster responsible for its biosynthesis from Streptomyces lasaliensis was identified. Then, Escherichia coli was engineered and cultivated under suitable conditions for the large-scale biosynthesis of echinomycin (31, 32).

Sato et al. (2013) successfully reconstituted the biosynthesis pathway using Escherichia coli non-ribosomal peptide synthetase. They declared that echinomycin-engineered biosynthesis by E. coli simplified the confirmation and usage of biosynthetic genes and enzymes, which were identified in other microorganisms that make up the biosynthetic pathways (33). Recently, Kojima et al. performed a retrosynthetic analysis of echinomycin. The study used Pummerer rearrangement of the sulfide moiety to the thioacetal group and rapid

cyclization of the C2-symmetrical depsipeptide ring with a sulfide linkage. They reported the first total synthesis of echinomycin (34).

3.3. Echinomycin mechanism of action

Echinomycin is a DNA bis-intercalator peptide with potent anticancer and antibacterial activity (17, 35). Initially, it was discovered as an antibacterial agent, and ten years later, its antitumor properties were described. In the 1970s, echinomycin's activity as a DNA bis-intercalator was first described, and the DNA binding sequence was identified as CpG. This bifunctional DNA intercalation is due to the presence of two quinoxaline chromophores. In 1974, echinomycin was introduced as the first bis-intercalator (14). Quinoxaline-2-carboxylic acid and 3-hydroxyquinaldic acid moieties in the quinomycin family gave it anticancer activity (16).

Echinomycin can enter the DNA through its major groove and bind in the minor groove (Figure 2) [1]. Echinomycin interacts and forms a stable complex with DNA through three different interactions: Van der Waals forces, hydrogen bonding, and intercalation. The peptide part of echinomycin is essential for strong and specific DNA binding; L-alanine of echinomycin forms a hydrogen bond with the guanine base pair of the 5'-CGTACG-3' sequence in the minor groove (31). Echinomycin was reported to cause a rearrangement of flanking A-T base pairs from Watson-Crick to Hoogsteen pairing when the sequence is 5'-ACGT-3'. NMR studies showed that not all the adjacent AT base pairs are exchanged for Hoogsteen pairing. Binding of echinomycin to [d(ACGTACGT)]2 causes both the internal and terminal AT pairs to be Hoogsteen pairing, while in [d(ACGTATACGT)]2, only the terminal AT pairs is Hoogsteen, and there is no Hoogsteen pairing in [d(TCGAACGT)]2 binding (11, 21).

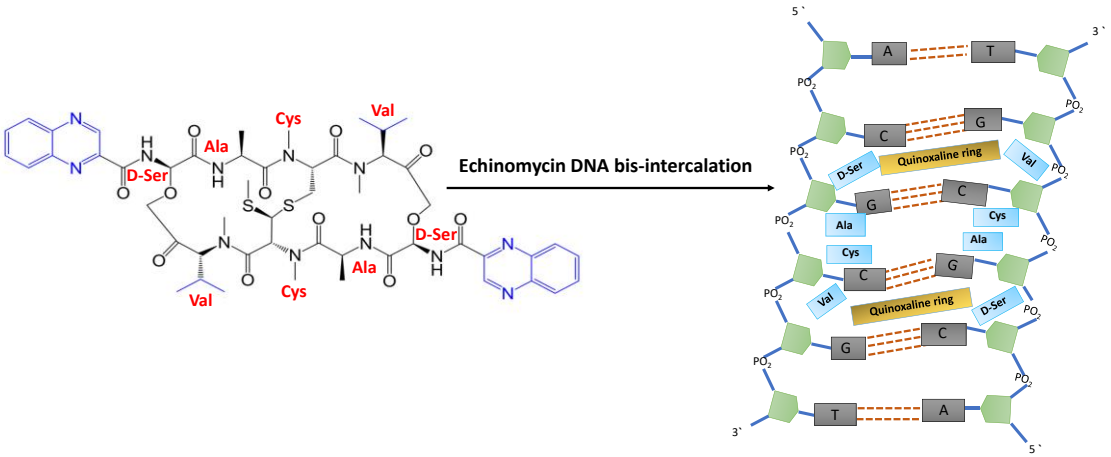

Figure 2: Echinomycin bis-intercalation into DNA

Footprinting method as well as NMR studies for quantitative analysis of echinomycin and DNA interaction revealed that their binding is a cooperative molecular recognition process (19). Cooperative bindging of echinomycin is induced by the DNA disruption cuased by the first echinomycin-DNA complex formed (figure 3). Cooperative binding depends on binding site and its adjacent sequence as in $[d(ACGTACGT)]_2$, $[d(TCGAACGT)]_2$ and $[d(ACGTATACGT)]_2$ parts (17, 21). Dissociation rates of echinomycin from DNA was determined by different kinetic studies. Echinomycin shuffles between different DNA sequences until best binding site is reached. Dissociation of echinomycin is the slowest from its optimal binding site (5'-ACGT-3') (17).

Biologically, DNA intercalating drugs, such as echinomycin, inhibit DNA-dependent RNA synthesis (transcription) and DNA replication. This is due to the inhibition of the separation of the DNA double helix and the prevention of RNA polymerase from binding to the DNA template (5, 7, 36).

White and Phillips (1989) studied the in vitro activity of echinomycin against a variety of RNA polymerases and found that transcription is terminated at the drug binding site. Moreover, a bidirectional transcription footprinting method was developed and found to be more sensitive and specific in determining drug-DNA binding sites than other footprinting methods (37).

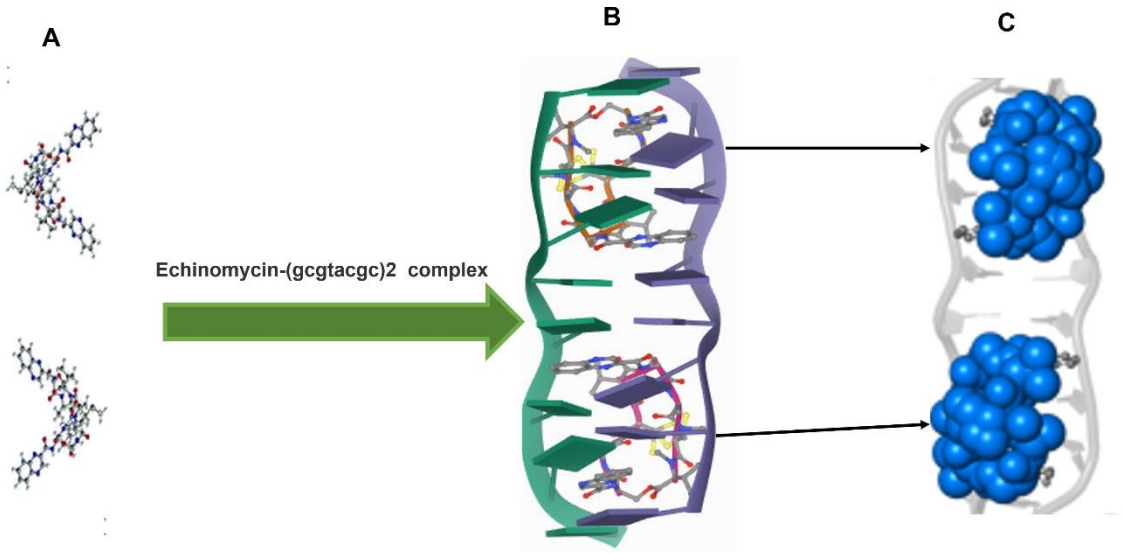

Figure 3: Crystallography mechanism of echinomycin DNA bis-intercalation A) Two molecules of Echinomycin B) show the two molecules intercalate and bind to (gcgtacgc)2 DNA sequence C) Structures of complexes between echinom viewed from the front (1)

Echinomycin specifically inhibits hypoxia-inducible factor-1 (HIF-1), a crucial factor in leukemia cell growth. Due to this inhibition, vascular endothelial growth factor (VEGF) production and the expression of antiapoptotic proteins Bcl-2 and Bcl-xL are reduced, leading to the inhibition of cell proliferation and apoptosis (Figure 4) (38). It also reduces and down-regulates many signaling pathways, including Notch signaling. Recently, echinomycin inhibited HIF-1-facilitated angiogenesis in a mouse model with choroidal neovascularization, which may offer hope for the treatment of neovascular age-related macular degeneration (39).

Interestingly, Park and his colleagues reviewed the toxicological profiles of echinomycin. They suggested that echinomycin could have great potential against human diseases. They demonstrated that echinomycin and its analogues control cellular proliferation through direct action on DNA, certain signaling pathways in mitochondria, and the inhibition of HIF-1α. The attractive echinomycin CG sequence specificity and irreversible binding increase its potency as anticancer therapy with no chemotherapeutic resistance (40).

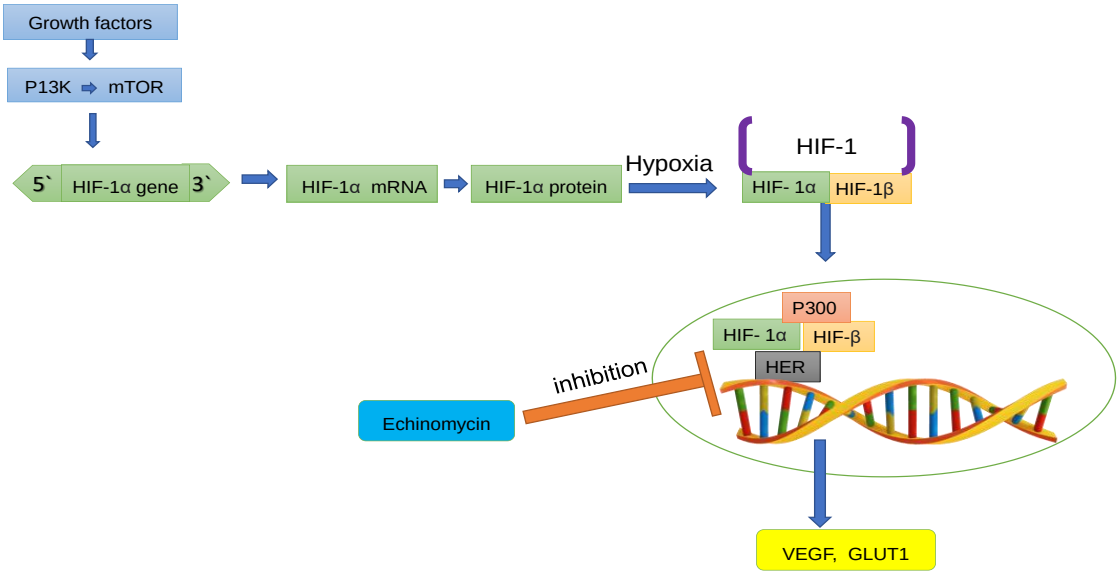

Figure 4: Mechanism of echinomycin inhibition of HIF-1α

Echinomycin has antimicrobial activity: antibacterial, antifungal, and antiviral (14). Echinomycin's inhibition of HIF-1 paved the way for developing treatments against fibrosis, cancer, obesity, infections, and autoimmune diseases (3, 41). Park et al. investigated the antimicrobial activity of echinomycin and compared it with vancomycin. They concluded that echinomycin has the potential to be used against S. aureus, which is resistant to vancomycin (42). The antimicrobial activity of echinomycin was explained by its interaction with bacterial circular DNA. Echinomycin's antibiotic activity was proven to interact selectively with specific DNA sequences in bacterial DNA (43).

4. THERAPEUTIC ACTIVITY

4.1. Echinomycin antibacterial activity

Many in vitro and in vivo assays have demonstrated that echinomycin has excellent activity against S. aureus, including methicillin-resistant Staphylococcus aureus (MRSA), which is equivalent to that of vancomycin, making it a choice for vancomycin-resistant S. aureus species (42). In vivo, echinomycin was more effective than vancomycin in a mouse model against Staphylococcus aureus (44). The in vitro antibacterial assay of echinomycin showed potent activity against several vancomycin-resistant Enterococci (VRE) clinical isolates (45). The good antibacterial properties of echinomycin against both Gram-positive and Gram-negative bacteria have encouraged efforts to synthesize and discover new quinoxaline derivatives. Echinomycin's activity against biofilm-forming MRSA and vancomycin-resistant Enterococcus faecalis was tested, and its minimum inhibitory concentrations (MIC) were found to be 0.03 µM against Staphylococcus aureus and 0.01 µM against Enterococcus faecalis (46).

4.2. Echinomycin antitumor activity

Recently, there has been a growing necessity and effort to develop new anticancer drugs to combat cancer resistance. In vitro, echinomycin has exhibited cytotoxic activity across diverse cell lines (21). Echinomycin advanced to phase I and II clinical trials for various cancer diseases, including endometrial carcinoma, ovarian cancer, soft tissue sarcoma, and others (Table 1) (6, 9, 47). However, the results demonstrated low or no efficacy, accompanied by serious side effects such as nausea, vomiting, reversible liver enzyme abnormalities, and allergic reactions (48).

Table 1: Timeline and evolution of echinomycin screening and investigation of therapeutic activity

Disease	Investigation	Formulation	Comments	Reference
Different tissue types/ Normal and cancer	*In vitro/* tumour colony-forming units	Echinomycin in ethanol	50% survival colony	(49)
B16 melanoma, and the P388 leukemia	Preclinical Murine/ dogs	Conventional formulation/ CrEL-based	Toxicity study /LD50	(50)
Advanced carcinoma	Phase I	Conventional formulation	Toxicity study/dose escalation	(51)
Advanced cancer	Phase I	Conventional formulation	Toxicity study/dose escalation	(52)
Squamous-cell carcinoma of the cervix.	Phase II	Conventional formulation	7% response	(47)
Metastatic cervix carcinoma	Phase II	Conventional formulation	No response	(53)
Advanced Ovarian cancer	Phase II	Conventional formulation	9% response	(47)
Advanced colorectal cancer	Phase II	Conventional formulation	No response	(54)
Stage IV recurrent or inoperable breast cancer	Phase II	Conventional formulation	4.6% response	(55)
Recurrent and metastatic nonsquamous cell carcinoma of the cervix:	Phase II	Conventional formulation	5.6% response	(48)
Recurrent and metastatic endometrial carcinoma	Phase II clinical trial	Conventional formulation	5% response	(9)
Renal cell carcinoma	Phase II clinical trial	Conventional formulation	5.6% response	(56)
Recurrent colorectal cancer	Phase II clinical trial	Conventional formulation	10% response	(57)
Soft tissue carcinoma	Phase II	Conventional formulation	No response	(6)
Metastatic Non-small Cell Lung Carcinoma	Phase II	Conventional formulation	5% response	(58)
leukaemia P388, melanoma B 16 and gastric SNU-16	*In vitro/ in vivo*	modified-echinomycin/ S-methylated sulfonium perchlorate of echinomycin	IC50 8-9 µg/ml For leukaemia P388, melanoma B 16 while gastric SNU-16 quite different need more studies	(59)
Xenopus sperm chromatin and cervical HeLa- S3cell nuclei *in vitro*	*In vitro: Xenopus sperm chromatin and HeLa cell nuclei / in vivo: embryos from Xenopus laevis*	In methanol and stored at –20°C	Anti- proliferative effects by inhibition of chromosomal DNA replication and embryonic development	(60)
HT-29 cells colorectal cancer cell line	*In vitro*	Organic solution	Apoptotic MAP kinases signalling pathways	(40)
U251 human glioma cells and MCF-7 cells	*In vitro*	Organic solution	Inhibited hypoxic induction of luciferase in cells and VEGF mRNA expression	(7)
Vancomycin-resistant enterococci	*In vitro*	Organic solution	MIC 0.125 µg/ml	(61)
Restenosis and thrombosis of echinomycin-eluting stents	*In vivo/pigs*	echinomycin-eluting stents topcoated with a hydrophobic heparin-polymer	effectively reduced both restenosis and thrombosis	(62)

Disease	Investigation	Formulation	Comments	Reference
Liver cancer HepG2 and cervical Hella cells	*In vitro*	Organic solution	dual effect on HIF-1 activity under normoxic and hypoxic conditions,	(10)
Clinical isolates of Staphylococcus aureus	*In vitro/ in vivo*	Organic solution	MIC 0.125 µg/ml	(42)
Biofilm-forming strains of Staphylococcus aureus Enterococcus faecalis.	*In vitro*	Organic solution	MIC 0.01- 0.03µM	(46)
Glioma stem cells lymphoma myeloid leukaemias (AML)	*In vitro*	Organic solution	regulate the tumorigenic capacity	(3)
Ovarian ovulation in mammalians	*In vivo*	Conventional formulation	Regulating gonadotropin-induced mammalian ovulatory process in vivo.	(63)
Leukaemia Cells lymphoma myeloid leukemia (AML)	*In vitro*	Organic solution	suppresses NOTCH1 signalling and suppress growth	(38)
Heterotopic ossification	*In vivo*	Echinomycin was diluted in dimethyl sulfoxide (DMSO) and administered subcutaneously	highly significant reduction in the bone volume	(64)
FKBP12 protein.	*In silico Docking*	Computer aid	echinomycin may have a double impact on HIF direct inhibition and through mTOR	(65)
Relapsed acute myeloid leukaemia without	Preclinical	Low dose echinomycin Organic solution	40% to 60%	(66)
Three pancreatic cancer cell lines, MiaPaCa-2, BxPC-3 and PanC-1/ tumour xenograft	*In vitro/ in vivo*	Quinomycin in 10% FBS	Significant inhibition of proliferation and colony formation in pancreatic cancer cell lines and tumour xenograft growth	(67)
Follicular Development in the Ovary of Postnatal Rats/ Granulosa cell culture	*In vitro/ in vivo*	Organic solution	Inhibition of follicular development	(68)
Endometriosis	Ectopic endometriotic tissues	Organic solution	100 nM decrease VEGF production	(8)
Adipogenesis in 3T3-L1 cells/white adipose tissue	*In vitro/ in vivo*	Organic solution	inhibited adipogenesis and body weight gain in high fat diet mice	(69)
Breast cancer	*In vitro/ in vivo*	Liposomal formulation	1200µg/m^2	(70)
H6OHDA induced Parkinson's disease model using SH-SY5Y human neuroblastoma	*In vitro/ In vivo*	Organic solution	Notch signalling pathway was decelerated and b-catenin stabilization was increased.	(71)

Disease	Investigation	Formulation	Comments	Reference
Glioblastoma	*In vitro*	Thermosensitive Liposomal- γ cyclodextrin formulation	IC50/1nM	(24)
Solid tumors/ metastatic breast cancer	*in vitro/ In vivo*	Liposomal formulation	Increase therapeutic index	(72)
Chromosome-negative myeloproliferative neoplasms	*Ex vivo* patient samples and *in vitro 32D cells*	Organic solution	Selectively decreased growth of JAK2V617F cells at 1 nM	(73)
Metastases of triple-negative breast cancer	*In vitro/ in vivo*	Liposomal formulation	Effective and less toxic than conventional formulations	(74)
Chemo-resistant Pancreatic Cancer	*in vivo*	syndecan-1 actively targeted nanoparticle	Autophagy-Mediated Death	(75)
Regresses tumour growth of lung cancer and lymphoma	*In vitro*	Organic solution	Cells were degraded through proteasome dependent pathways	(76)
Age-related Macular degeneration	*In vitro/ in vivo*	Organic solution	Significantly decreased vascular lesion	(39)
Breast cancer and Lung cancer	*In vitro*	Antinucleon aptamer targeted pH-sensitive- γ cyclodextrin- liposomes	IC50 MCF7, 0.46 nM MDA-MB-231, 0.18 Nm A549 0.92nM	(77)

However, Huang et al. investigated the antitumor activity of echinomycin against lung cancer and lymphoma in vitro and in vivo. They proposed that echinomycin instantaneously inhibited MYC and HIF1α, leading to a reversal in tumor cell growth (76). In May 2015 and 2017, the OncoImmune company manufactured echinomycin and received orphan drug designations for treating myeloid leukemia (AML) and graft-versus-host disease (GVHD) in the U.S.A., respectively.

5. Echinomycin drug delivery and dosage forms

The peptide nature and extreme lipophilicity constitute the main obstacles to properly formulate echinomycin into a pharmaceutical dosage form (15). Consequently, echinomycin was formulated as a conjugate with Cremophor EL, a non-ionic emulsifier produced by the reaction of ethylene oxide and castor oil to solubilize hydrophobic drugs (78). In many drug formulations, such as echinomycin, Cremophor EL has been known to cause allergic and hypersensitivity reactions (78). It is believed that the use of Cremophor EL was one of the factors that led to the discontinuation of echinomycin clinical trials (72). Recently, nanoparticle drug delivery systems (79) have become suitable for all compounds with low water solubility and high toxicity (80).

Wang et al. developed a liposomal formulation of echinomycin. The hydrophobic echinomycin was encapsulated into the liposome bilayer, and they proposed that the new formulation enhanced the drug's physicochemical properties and decreased its toxicity (72). In another study, echinomycin was complexed with γ-Cyclodextrin, and the inclusion complex was encapsulated inside PEGylated thermosensitive liposomes and tested for their cytotoxicity using a Glioblastoma cell line (81). Meanwhile, Bailey et al. studied the activity of the liposomal echinomycin formulation on triple-negative breast cancer in vitro and in vivo. They reported that liposomal echinomycin is a more potent inhibitor of HIF-1α transcriptional activity in primary and metastasized cells in vivo (74).

In a further study, liposomes encapsulating echinomycin were fabricated using a PEGylated phospholipid, a neutral phosphoglyceride, and a sterol for treating patients who show

overexpression of HIF-1α and/or HIF-2α. Additionally, echinomycin PEGylated liposomal formulation has promising potential for the treatment of many diseases, including proliferative diseases, autoimmune diseases, and graft-versus-host disease (7).

Another pH-sensitive liposomal formulation functionalized with an antinucleon aptamer was tested in vitro using various cancer cell lines. Aptamer-targeted pH-sensitive PEGylated liposomes were designed, formulated, and fully characterized. These liposomes remained stable at physiological pH and released their payload at low pH. These innovative liposomes exhibited excellent selectivity and cytotoxicity against three cancer cell lines: MCF7, MDA-MB-231 breast cancer, and A549 lung cancer cell lines (77).

6. Conclusion and future insights

Echinomycin possesses a unique structure, an intriguing mechanism of action, and promising potential as both an antimicrobial and anticancer therapy. Nanoliposome formulations have demonstrated enhanced potency and selectivity while mitigating side effects. Researchers will continue their exploration of echinomycin, aiming to address the main challenges associated with this promising drug. These challenges encompass various aspects, including the development of cost-effective production methods and the improvement of its bioavailability.

Conflict of interest: the authors declare no conflict of interest.

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عقار الإكينوماسين: رحلة التحديات

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ملخص

الإكينومايسن هو مركب طبيعي تم اكتشافه وعزله من البكتيريا وتم تقديمه كمضاد حيوي وعلاج مضاد للسرطان. ومع ذلك، فقد فشل سريريًا بسبب التركيبات غير الصحيحة وسرعة تحطيمه في الجسم. بعد التجارب السريرية غير الناجحة، تم وقف التجارب السريرية عليه في الآونة الأخيرة، أعطت آلية جديدة بعض الأمل في إحياء مادة الاكينوميسين كمثبط للعامل ((HIF-1 المحرض لنقص الأكسجين، و في عام 2015 إكينوميسين وصف لعلاج ابيضاض الدم النخاعي الحاد في الولايات المتحدة الأمريكية. علاوة على ذلك، أتاحت التطورات في أنظمة توصيل الأدوية آفاقًا جديدة للتغلب على مشكلات تركيبة الإكينومايسين واستكشاف المزيد من الفوائد العلاجية. توضح هذه المراجعة تفاصيل رحلة إيكينومايسين إلى جانب التحديات الرئيسية لهذا الدواء الفعال وتقدم رؤى حول التطبيقات السريرية المحتملة في المستقبل.

الكلمات الدالة: إكينومايسين، روابط مستهدفة، ببتيدات دورية، مضاد حيوي كينوكسالين، مقسم ثنائي الحمض النووي.

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