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Review Article

TUBEIMOSIDE-1, A TRITERPENOID SAPONIN: AN UPDATE ON ITS PHARMACOLOGICAL EFFECTS

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ABSTRACT

It is known that humans have been using natural products for medicinal use for ages. Tubeimoside-1 (TBMS1) is a triterpenoid saponin first isolated in China from Bolbostemma paniculatum (Maxim) Franquet, Cucurbitaceae. This review provides a deep overview on TBMS1 and extensively summarizes its pharmacological functions. As result, TBMS1 has drawn great interest in medicinal field due to its multiple pharmacological functions such as anticancer, anti-inflammatory, antitumor, antidiabetic, anti-human immunodeficiency viruses, and neuroprotective properties. Further, TBMS1 plays an important role in a wide range of pharmacological processes. Although possessing important functions, further experimentations are required to broaden the scope of its application.

Keywords: Tubeimoside-1, Pharmacological activities, Natural compounds.

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INTRODUCTION

Plants have been used as a source of medicine throughout history and continue to serve as a basis for many pharmaceuticals used today [1]. Natural products having been known as one of the most important sources of potential drug leads [2-4] and continue to provide structural diversity. They have a long tradition as valuable starting points for medicinal chemistry and drug discovery [5]. Their use as medicines has been described throughout history in the form of traditional medicines, remedies, potions, and oils. The main source of knowledge about the use of natural plant products is the result of human experimentation through trial and error over hundreds of centuries [6]. Many researches worldwide are focusing on natural products for the discovery of new compounds.

Rhizoma bolbostemmatis (Chinese name "Tu Bei Mu"), the tuber of *Bolbostemma paniculatum*, is a traditional Chinese medicine. It has been used to treat acute mastitis, inflammation, and snake venoms in Qing Dynasty. In Sichuan and Shanxi (China), Bolbostemae rhizome is considered as a traditional Chinese herb effective in the treatment of esophagus and stomach cancer [7]. Tubeimoside-1 (TBMS1) (Fig. 1), a triterpenoid saponin, was purified from this plant in 1986 for the 1st time [8]. As Chinese medicine monomer with a high yield and water solubility, TBMS-1 is used to treat mammary carbuncles, scrofula, and phlegm nodes [7]. Our objective is to update the knowledge about TBMS1 and its pharmacological effects that will be useful to scientists working in the field of natural compounds.

NATURAL SOURCES OF TBMS-1

TBMS-1 (Fig. 2) is extracted from the tuber of *B. paniculatum* (Maxim) Franquet (*Cucurbitaceae*) [8]. *R. bolbostemmatis,* also known as "Tu Bei Mu" in Chinese, is the dry tuber of *B. paniculatum* (Maxim.) [9].

BIOLOGICAL/PHARMACOLOGICAL FUNCTIONS OF TBMS1 AND ITS MECHANISMS OF ACTION

Growing studies have reported that TBMS1 is known to show considerable pharmacological properties such as anti-cancer, anti-human immunodeficiency viruses (HIV) [10], anti-inflammatory [8,11,12], anti-tumor, and anti-tumorigenic activities [11].

Anti-inflammatory activity (Table 1)

Inflammation, a defense mechanism, is an immediate response of a body to tissue damage caused by pathogens, toxic stimuli (physical or chemical injury), or any other cause. Although inflammatory response is a defense mechanism, if persistent, it can put person at increased risks of developing multiple pathological conditions such as cancer, allergy, atherosclerosis, rheumatoid arthritis, and autoimmune diseases [13]. The negative side effects associated with nonsteroidal anti-inflammatory drugs are triggering the need for researchers to find effective and safe alternatives [14]. The authors, therefore, carried out a study to provide more evidence of the protective effects of TBMS1 on pathological conditions such as rheumatoid arthritis. They first found that the concentrations of Astilbin and TBMS1 in the n-butyl alcohol fraction of this couple drug are, respectively, 13.13% and 3.4%. The results of their analysis showed that the drug couple exhibited considerable inhibitory activity on the paw edema model with lowered levels of interleukin (IL)-1β, IL-6, and tumor necrosis factor-alpha (TNF-α). The authors concluded that the natural product possesses a potential to be established as a new therapeutic agent [15]. In collagen-induced arthritis rats, TBMS1 treatment attenuated the inflammation and the destruction of the rats' joints. On the other hand, *in vitro* studies also revealed that TBMS1 has capability to suppress the production of pro-inflammatory cytokines including IL-1β, IL-6, IL-8, and TNFα, downregulate the expression of matrix metallopeptidase 9. Mechanistic analysis demonstrated that TBMS1 inhibited TNFα-induced activations of nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (p38 and c-Jun N-terminal kinase [JNK]). This inhibition resulted in down-regulation of pro-inflammatory cytokines, which has a beneficial effect for anti-proliferative and anti-migratory activities of fibroblast-like synovial cells [16]. TBMS1 at concentrations of 5–100 μmol/L has been known to suppress the viability of DU145 and P3 cells, induced apoptosis and cell cycle arrest at Gap0/Gap1 (G0/G1) phase. In DU145 cells, TBMS1-induced mitochondrial apoptosis, modulated B-cell lymphoma 2 (Bcl-2) family protein and cleaved caspase-3, and activated apoptosis signal-regulating kinase (ASK-1) and its downstream targets p38 and JNK [17].

In lung injury, the effects of TBMS1 and its mechanisms of action were investigated. As results, treatment with TBMS1 attenuated the development of pulmonary injury. Its mechanisms of action were

associated with reducing cytotoxic effects, levels of inflammatory mediators, and oxidative damage, indicating that TBMS1 is a potential therapeutic drug for treating lung injury [18]. In 2013, our laboratory investigated the protective effect of TBMS1 on inflammation in lipopolysaccharide (LPS)-stimulated RAW 264.7 cells and a LPS-induced *in vivo* lung injury model. Our results showed that TBMS1 inhibited the production of the pro-inflammatory cytokines, TNF-α, IL-6, and IL-1β *in vitro* and *in vivo*. Pre-treatment with TBMS1 attenuated the development of pulmonary edema, histological severities, and inflammatory cells infiltration in mice with lung injury. In addition, we further demonstrated that TBMS1 exerts an anti-inflammatory effect *in vivo* model of acute lung injury through suppression of nuclear factor of kappa light polypeptide gene enhancer in B-cells activation and p38/extracellular signal-regulated kinase mitogen-activated protein kinases signaling [19]. In other research, TBMS1 also inhibited the proliferation of L-02 cells. This growth inhibition of L-02 cells was accompanied by the collapse of mitochondrial membrane potential, release of cyt-c from the mitochondria to the cytosol, and activation of caspase-9 and -3. This observation indicates an apoptosis through the mitochondrial pathway and may be significant to clinical applications [20].

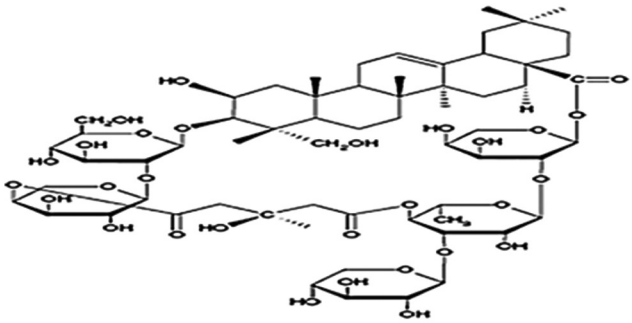

Fig. 1: Chemical structure of tubeimoside

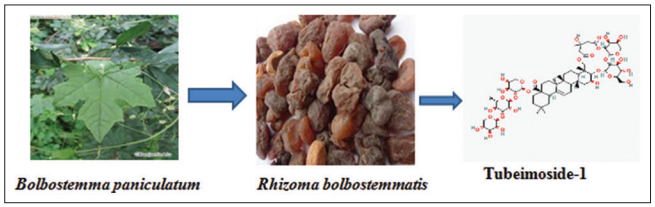

Fig. 2: Natural source of tubeimoside 1

Sepsis is a disease with high mortality rate worldwide. During the disease, inducible nitric oxide synthase (iNOS)-induced vascular hyporeactivity plays a key role. In recent study, Luo *et al*., 2020, investigated other effects of TBMS1 and found that TBMS1 (4 mg/kg) intraperitoneally injected 1 h before cecal ligation and puncture partially improved survival, ameliorated mean arterial pressure, and enhanced vascular responsiveness to norepinephrine and chlorure de potassium in wild-type septic mice. Furthermore, the activated toll-like receptor 4 (TLR4)-myeloid differentiation primary response 88 (MyD88)-NF-κB-iNOS pathway was attenuated by TBMS1 both *in vitro* and *in vivo*. The authors concluded that TBMS1 may protect mice in sepsis by reducing excessive nitric oxide production through inhibiting the TLR4-MyD88-NF-κB-iNOS pathway [21].

Parkinson's disease (PD) is a common neurodegenerative disease in middle-aged and elderly people, and characterized clinically by resting tremor, bradykinesia, rigidity, and postural instability. It has been shown that microglia-mediated inflammation may play an important role in the neurodegenerative process [22-35]. Therefore, authors investigated whether TBMS1 could protect dopaminergic neurons by inhibiting the activation of microglia in LPS-induced PD rat model. During their study, the effect and mechanism of TBMS1 on neuroinflammation were assessed in LPS-exposed murine microglial BV-2 cells. The results *in vivo* showed that TBMS1 suppressed microglial activation and dopaminergic neuron reduction. *In vitro* study found that TBMS1 could inhibit LPS-induced inflammatory responses in BV-2 cells, and this effect was mediated by suppressing the phosphorylation of protein kinase B (AKT), (NF-κB p65), p38, and extracellular regulated protein kinases (ERK1/2) [36].

Antidiabetic activity

Diabetes mellitus is a complex and serious multifactorial disease characterized by hyperglycemia and glucose intolerance, due either to a relative deficiency in insulin secretion or to an alteration in the effectiveness of insulin action to promote glucose uptake [37-40]. Different types of medicinal plants are used to treat diabetes mellitus. For the treatment of diabetes, before insulin became available, the only options were those based on traditional approaches [41-55]. Among them, Yang *et al.* (2020) found that TBMS1 ameliorated the decrease of bone mass in type 2 diabetes-induced osteoporosis in rats. It appears that TBMS1 provides this protective activity through the inhibition of osteoclast formation and function. In addition, TBMS1 has been shown to inhibit transcriptional activation of NF-κB and degradation of IκBα. Collectively, the results demonstrate that TBMS1 attenuates osteoclastogenesis through downregulation of the NF-κB signaling pathway. In conclusion, this natural product may be a potential candidate for the treatment of bone-destroying diseases such as osteoporosis in type 2 diabetes [56].

Table 1 : Anti-inflammatory activities *in vitro* and *in vivo*

Assay	Organisms tested	Concentrations	Molecular targets	References
Carrageenan -induced paw edema	Rats	0.05–1.6 mg/mL	IL-1β, IL-6, and TNF-α	[15]
LPS-injected Parkinson's disease	Rats	1, 2, and 4 mg/kg/day	TH protein level, OX-42,	[36]
LPS-exposed murine microglial	BV-2 cells	1, 2, and 4 μM	IL-6, IL-1β, TNF-α, iNOS, COX-2 AKT, NF-κB p65, p38, and ERK1/2	[36]
Collagen -induced arthritis	Rats		No effect on the phosphorylation of JNK1/2 NF-κB, MAPKs (p38 and JNK)	[16]
Effects on synoviocytes	FLS cells		IL-1β, IL-6, IL-8 TNFα, MMP-9, NF-κB, and MAPKs (p38 and JNK)	[16]
LPS-stimulated RAW 264.7 cells	RAW 264.7 cells	2–6 mM	TNF-α, IL-6, IL-1β IκB, and p38	[19]
LPS-induced *in vivo* lung injury	BALB/c Mice	1, 2 or 4 mg/kg	TNF-α, IL-6, IL-1β, IκB, and p38	[19]
Particulate matter -induced pulmonary	BALB/c mice	45–180 mg/kg	TNF-α and IL-6 MDA, NO, iNOS, and SOD	[18]
Role in protecting dopaminergic neurons	Rats	1,2,4 mg/kg/day	AKT, NF-κB p65, and p38 ERK1/2	[36]

SOD: Superoxide dismutase, COX-2: Cyclooxygenase-2, MAPKs: Mitogen-activated protein kinases, PD: Parkinson's disease

Table 2: Anticancer activities of TBMS-1 *in vitro* and *in vivo*

Assay	Organisms tested	Concentrations	Molecular targets	References
Effect against cervical cancer cells	HeLa and SiHa cells	5–30 uM	AMPK	[58]
	Mice	3 mg/kg	AMPK	[58]
Inducing *in vitro* and *in vivo* macropinocytosis	SW480, DLD-1 and HCT116	8 uM	Caspase 3 and PARP	[59]
Effect on autophagy	HeLa cells		Akt-mTOR-eEF-2K	[80]
Effect on proliferation and metastasis	NCI-H1299 cells	10 μM	VEGF)-A/VEGFR2/ERK	[57]
Effect on the proliferation, metastasis, and apoptosis *in vitro*	CAL27 and SCC15 cells	10 μM	PARP, p-ERK1/2, Bcl-2, caspase-3, 7 and 8 and 9, PARP, c-Myc, and MMP-7	[89]
CXCR4-mediated metastasis of breast cancer	MDA-MB-231, MDA-MB-435, T47D, and MCF-7 cells	5 μM	NF-κB	[63]
Role on human colorectal cancer	HCT-8 cells	10, 20, and 50 μg/ml	Wnt/β-catenin	[65]
Anticancer activity and molecular targets in human prostate cancer cells *in vitro*	DU145 and P3 human prostate cancer cells	5-100 μmol/L	Bcl-2, caspase-3, ASK-1, p38, and JNK	[17]
Effect against lung cancer	NCl-H460 and A549 cells	5–50 μM	VEGFR2, Tie2, and AKT/mT	[66]
	Nu/nu mice	5 mg/kg		
	NCI-H460 lung cancer cells	20 μM	p53/MDM2, mTOR, and NF-κB	[67]
Mechanism of its cytotoxic effect on EC109 cells	EC109 cells	45 μmol/L	P21-cyclin, B1/cdc2 G2/M cell cycle arrest	[68]
Effect on human gastric cancer cells	BGC823 cells	0–10 μmol/L	Bcl-2	[90]
Cytotoxic effect and apoptosis mechanism	HepG2 cells		Caspase-3, -8, and -9, Fas, Fas ligand, Bcl-2, Bak, Bax, TNF-α, NF-κB, JNK, and p53	[81]
Pro-apoptotic activity against SKOV-3 cell lines	SKOV-3 cell lines	2, 4, 8, and 16 μM	ERK 1 and 2, Bcl-2/Bax caspase-3, and Ca^{2+}	[91]
Effect in cisplatin-resistant human ovarian cancer cells	A2780/DDP cells	8 μmol/L	Ca2+ , Bcl-2, GST-π mRNA, ERK, and p381	[92]
Effect in human choriocarcinoma JEG-3 cells	JEG-3 cells	6 μM	Bax, Bcl-2, rNF-κB, p38/MAPK, ERK1/2, PI3K/Akt	[93]
Effect in apoptosis-mediated cell death	HepG2 cells	10, 20, and 30 μM	Caspase-3 and -9 Bax and Bcl-2	[94]
Effect on the apoptosis of human nasopharyngeal carcinoma cell line CNE-2Z	CNE-2Z cells	10, 30, 40, 50, and 60 μM	bcl-2 and bax	[95]
Effect on cell proliferation, cell cycle, and apoptosis	A375 cells	20 and 40 μM	Bcl-2, Bax	[96]
Antiproliferative effects in human bladder cancer T24 cells	T24 cells	10 and 20 μM	Bcl-2, Bax, and p21	[97]
Pathways involved in induced cytotoxicity	HeLa cells		ROS and Ca(2+) r, CyclinB1, Cdc2, and Cdc25C	[98]
Effect on lung cancer cell growth	A549 and PC9 cells	4–32μM	MAPK-JNK, AP-1, NF-κB and TNFα	[76]

ROS: Reactive oxygen species, AMPK: 5' adenosine monophosphate-activated protein kinase

Anticancer activity (Table 2)

Cancer is a disease of multicellular organisms that is characterized by the uncontrolled multiplication of subtly altered normal human cells [57-60]. As many as, 89% of patients with cancer or other chronic conditions use alternative therapies, often herbal or natural products, and 75% are secretive about alternative product use [61-69].

Given the remarkable chemical diversity in nature, natural products are considered as a rich reservoir of bioactive compounds with therapeutic potentials [70,71].

The number produced by plants has been estimated to be between 500,000 and 600,000. With regard to biological activity, there are about 200,000–250,000 biologically active products (active and/or toxic) [72-75].

Anticancer activity is the effect of natural and synthetic or biological and chemical agents in reversing, eliminating, or preventing cancerous progression. The development of cancer registries worldwide has led to the search for new drug candidates that are toxic to cancer cells while having no harmful effect on normal cells. Thus, the investigation of natural products is an area of high interest [61-63].

TBMS1 is known as a novel compound with anticancer activity by inhibiting the growth of several cancer cells including lung cancer [76]. Its effect of TBMS1 on the metastasis of nonsmall cell lung cancer and underlying mechanisms has been investigated. The above results indicate that TBMS1 inhibits proliferation and metastasis, and contributes to apoptosis of NCI H1299 cells, which may be induced by overexpression of miRNA 126 5p, which inactivates the VEGF A/vascular endothelial growth factor receptor-2 (VEGFR2)/ERK signaling pathway. Thus, TBMS1 may be considered as a very promising drug for the prevention and treatment of non-small cell lung cancer [77]. Islam *et al*. (2019) explained that TBMS1 has long been widely used in the treatment of various ailments (including cancer) in traditional Chinese medicine. In support of this statement, evidence of TBMS1 anticancer activities has been provided at different stages of carcinogenesis in *in vitro* and *in vivo* models. For example, it could inhibit cell growth and proliferation and induce cell differentiation, apoptosis, and autophagy. It inhibits inflammatory responses and suppresses angiogenesis, invasion, and metastasis through various signaling pathways [9].

Strikingly, TBMS1 as a novel lethal impaired autophagolysosome inducer might enhance the therapeutic effects of chemotherapeutic drugs toward cervical cancer, such as cisplatin and paclitaxel [78].

Extensive research revealed that TBMS1 could induce inhibition of proliferation and cell death of cervical cancer cells both *in vitro* and *in vivo*. Further results showed that treatment with TBMS1 could induce the accumulation of autophagosomes, which is an important factor for TBMS1 against cervical cancer cells. It increased autophagosome by two pathways: It first initiates autophagy by stimulating 5' adenosine monophosphate-activated protein kinase (AMPK) which would lead to stabilization of the Beclin1-Vps complex through dissociation of Bcl-2 from Beclin1; on the other hand, it could interfere with lysosomal cathepsin activity and block autophagic flux, leading to the collection of impaired autophagolysosomes. In colorectal cancer (CRC), it induces macropinocytosis *in vitro* and *in vivo* [79]. Activation of autophagy by the natural substance has been shown by the increase in LC3-II and GFP-LC3 spots, the observation of autophagosomes, and the increase in autophagic flux. In three human breast cancer cell lines, the authors demonstrated that the Akt-mammalian target of rapamycin (mTOR)-eukaryotic elongation factor 2 kinase pathway has been involved in the activation of TBMS1-induced autophagy. In these studies, it has been observed that autophagy inhibition enhanced the cytotoxic effect of the product by promoting apoptosis, suggesting that inhibition of cytoprotective autophagy may be a therapeutic strategy to enhance the protective activity of TBMS1 against cancers [80]. Mechanism studies established that TBMS1 induces phosphorylation of apoptosis signal regulatory kinase 1 and its proteins (JNK and P38). The reported data confirmed that TBMS1 can induce oxidative stress-mediated apoptosis and G2/M phase arrest in HepG2 liver cancer cells through NF-KB, JNK, and p53 pathways [81,82].

A research evaluating the effect of TBMS1 on breast cancer metastasis was done in a metastasis model of nude mice and TBMS1 was shown to suppress the CXCR4-mediated metastasis of breast cancer by inhibiting NF-κB-binding activity [83]. Acting as the main active ingredients in the extract of *R. bolbostemmatis*, TBMS1, and acetylbenzoylaconine (at 10:10 μg/mL and 5:2.5 μg/mL) also produced inhibitory effects on the proliferation and migration of malondialdehyde-MB-231 and SKBR3 cells [84]. In addition, the role of TBMS1 on human CRC and its underlying mechanism was explored. In the study, TBMS1 inhibits the proliferation, migration/invasion of CRC cells, and reduces β-catenin expression. The authors demonstrated that TBMS1 inhibited CRC cell proliferation and invasion through suppressing the Wnt/β-catenin signaling pathway [85]. Studying the anticancer activity and molecular targets of TBMS1 in human prostate cancer cells *in vitro*, authors remarked that TBMS1 (5–100 μmol/L) significantly suppressed the viability of DU145 and P3 cells with half maximal inhibitory concentration values of approximately 10 and 20 μmol/L, induced apoptosis, and cell cycle arrest at G0/G1 phase in DU145 and P3 cells. In DU145 cells, it induced mitochondrial apoptosis, evidenced by r*eactive* oxygen species (ROS) generation, mitochondrial dysfunction, endoplasmic reticulum stress, modulated Bcl-2 family protein and cleaved caspase-3, and activated ASK-1 and its downstream targets p38 and JNK. In lung cancer, results showed that TBMS1 stimulates proteasomal degradation of VEGFR2 and Tie2 in endothelial cells, which is found to downregulate AKT/mTOR signaling [86]. Its precise mechanism involved nucleolar stress-induced p53/murine double minute clone 2 (MDM2), mTOR, and NF-κB signaling pathways [87]. Biochemical studies of the drug showed that TBMS1-induced molecular events were related to mitochondria-induced intrinsic apoptosis and P21-cyclin B1/cdc2 complex-related G2/M cell cycle arrest [88].

Neuroprotective activity

It has been confirmed that dopaminergic neurons are damaged during PD. The authors first investigated whether TBMS1 could protect dopaminergic neurons and then evaluated its mechanism of action. *In vivo* results showed that TBMS1 was able to suppress microglial activation and reduction of dopaminergic neurons in the LPS-injected PD rat model. Overall, these results demonstrated that TBMS1 played a role in protecting dopaminergic neurons by inhibiting microglia-mediated neuroinflammation [36].

Anti-HIV effect

As the risk of HIV infection continues to increase, effective therapeutic approaches are essential to ensure the recovery of infected patients [99,100]. To determine whether TBMS1 has anti-infective activity against human HIV, the authors evaluated its effects on the HIV core protein p24 and on HIV-mediated cytopathogenesis. As results, TBMS1 inhibited both p24 production and cytopathogenesis mediated by human T-cell lymphotropic virus-IIIB. Therefore, the authors concluded that TBMS1 had an inhibitory action on the infection of HIV-1 isolates and would be a promising candidate for treatment of acquired immune deficiency syndrome [101,102].

Antitumor functions

Authors have tested and demonstrated with low toxicity the antitumor activity of TMBS1 in different tumors such as promyelocytic leukemia, lung cancer, cervical cancer, nasopharyngeal carcinoma, and esophageal carcinoma [103]. They observed that TMBS1 may induce a mitochondria-related apoptotic pathway and cell cycle arrest in cervical carcinoma, ovarian cancer, choriocarcinoma, and glioma [91,93,104], inhibits the growth and invasion of CRC cells, and is effective in combination

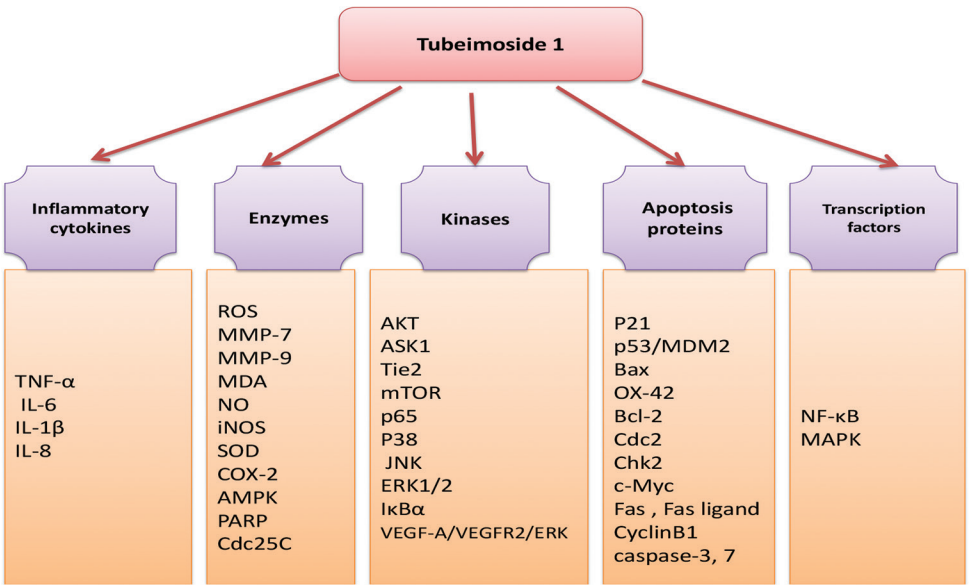

Fig. 3: Major molecular targets and mechanism of action of tubeimoside-1

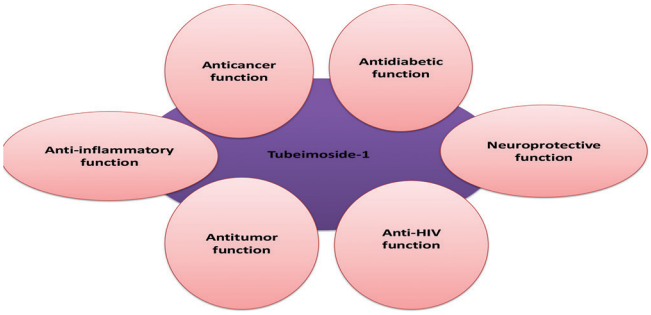

Fig. 4: Pharmacological effects of tubeimoside-1

therapies, particularly at targeting drug-resistant cancerous cells [9]. TBMS1 treatment could either promote autophagy initiation by ROS-induced AMPK activation, or block autophagy flux through inhibiting lysosomal hydrolytic enzymes [11,105].

PHARMACOKINETICS AND BIOAVAILABILITY STUDY

In a recent study, the authors aimed to establish and validate a rapid, selective, and sensitive ultra-performance liquid chromatography-tandem mass spectrometry method to determine the outcome of TBMS1 in mouse whole blood and its application in studying pharmacokinetics and bioavailability. The lower limit of quantitation for TBMS1 was 2 ng/mL, and the calibration curve ranged linearly from 2 to 2000 ng/mL. The relative standard deviation of interday and intraday precision was <15%, and accuracy ranged from 91.7% to 108.0%. The mean recovery was >66.9%, and the matrix effects were 104.8% to 111.0% [106].

CONCLUSION AND FUTURE PERSPECTIVES

TBMS1, the tuber of *B. paniculatum* (Maxim) Franquet (*Cucurbitaceae*), is a traditional Chinese herb. The extract has been reported to possess various pharmacological functions such as anticancer, anti-HIV, anti-inflammatory, antitumor, antidiabetic, and neuroprotective activities. Our review supports the hypothesis that many pathways, mediators, and receptors are involved in TMBS1-induced effects (Figs. 3 and 4). Although TMBS1 is well known for its various pharmacological applications, several *in vitro* and *in vivo* researches are needed to further the medical knowledge on TMBS1 as agent for the prevention and treatment of various diseases.

AUTHORS' CONTRIBUTIONS

All the authors have contributed significantly to the study.

CONFLICTS OF INTEREST

Authors did not have any conflict/competing interests.

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