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Review article

An insight into the anticancer potentials of lignan arctiin: A comprehensive review of molecular mechanisms

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ABSTRACT

Natural products are being developed as possible treatment options due to the rising prevalence of cancer and the harmful side effects of synthetic medications. Arctiin is a naturally occurring lignan found in numerous plants and exhibits different pharmacological activities, along with cancer. To elucidate the anticancer properties and underlying mechanisms of action, a comprehensive search of various electronic databases was conducted using appropriate keywords to identify relevant publications. The findings suggest that arctiin exhibits anticancer properties against tumor formation and various cancers such as cervical, myeloma, prostate, endothelial, gastric, and colon cancers in several preclinical pharmacological investigations. This naturally occurring compound exerts its anticancer effect through different cellular mechanisms, including mitochondrial dysfunction, cell cycle at different phases (G2/M), inhibition of cell proliferation, apoptotic cell death, and cytotoxic effects, as well as inhibition of migration and invasion of various malignant cells. Moreover, the study also revealed that, among the various cellular pathways, arctiin was shown to be more potent in terms of the PI3K/AKT and JAK/STAT signaling pathways. However, pharmacokinetic investigation indicated the compound's poor oral bioavailability. Because of these findings, arctiin might be considered a promising chemotherapeutic drug candidate.

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1. Introduction

Cancer is recognized as a heterogeneous ailment and ranks as one of the primary contributors to morbidity and mortality worldwide [1,2]. Cancer is characterized by the anomalous and unregulated proliferation of certain cells in the body, capable of metastasizing and infiltrating surrounding tissues and organs [3]. Cancer may affect a wide range of organs inside the human body, including almost all major organ systems. Extensive research has identified around 100 separate disorders that might manifest as compensatory responses to the deleterious effects of cancer [4]. According to the World Health Organization (WHO), the worldwide death rate from cancer in 2020 was expected to be 10 million, with lung cancer being responsible for 1.80 million of these fatalities (https://www.who.int/health-topics/cancer, accessed on December 01, 2023).

The mechanisms that are responsible for the formation of malignant or abnormal cells are very complicated, and their development is the consequence of a variety of environmental and genetic factors [5]. Epigenetics is the study of alterations in inheritable gene expression that cause abnormal cell growth, development, and regulation. This disruption encompasses impaired apoptosis, the initiation of angiogenesis, and the metastasis of unaffected tissues or organs, all of which collectively contribute to the development of cancer [6,7]. The dysregulation of the phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/m-TOR), Janus kinase/Signal Transducer and Activator of Transcription (JAK/STAT), and extracellular signal-regulated kinase (ERK) signaling pathway is of significant importance in the development of various cancer types [8,9]. The development of cancer is seen as a multi-stage process at the molecular level, including the occurrence of mutations and subsequent selection for cells exhibiting progressively enhanced abilities to survive, proliferate, invade, and metastasize. Tumor clonality, which refers to the proliferation of neoplastic cells originating from a single cell and exhibiting aberrant development, represents the first phase of tumorigenesis. One indication of the disease's progression occurring through various stages is the observation that most tumors manifest in individuals throughout their older years [10–12].

A range of lifestyle variables, such as bad eating habits, excessive alcohol use, smoking, a lack of physical activities, and catching other diseases, all increase the possibility of developing cancer [12,13]. The American Cancer Society (ACS) provides food and exercise recommendations to inform the general public and healthcare practitioners about healthy eating habits and other lifestyle choices that reduce the risk of cancer [14]. In the management of cancer, a range of medical treatments are used, including chemotherapeutic agents, radiation therapy, and surgery. Chemotherapy, an effective modality in the treatment of cancer, involves the use of chemical substances, either from natural sources or synthesized compounds, that effectively impede the proliferation of cancer cells by either inducing their destruction or inhibiting their division [15–17]. Nevertheless, it is important to acknowledge that these procedures may result in significant adverse reactions when used in the context of cancer therapy. Patients may have been presented with persistent infertility, alopecia, oral ulcers, cardiac anomalies, myelosuppression, and cardiovascular abnormalities. In addition, the occurrence of bone marrow toxicities leads to the development of anemia and a reduced ability to effectively battle pathogenic infections. Nausea and vomiting are often regarded as very undesirable adverse effects experienced by those undergoing cancer treatment [18,19]. Hence, it is essential to identify viable chemotherapeutic agents that might impede the proliferation of cancer cells while minimizing unwanted effects.

Lignans, polyphenolic compounds found in plants, constitute a class of chemicals that are synthesized by the condensation of phenylpropane molecules. These compounds are widely distributed in various seeds, legumes, fruits, and vegetables [20]. Lignans have many roles in the physiology of plants, and their varied functionalities hold considerable importance for a wide array of organisms, including humans [21,22]. They are primarily responsible for the defensive mechanism and are identified in their chemical structure by the presence of two terminal phenyl groups [23]. Lignans have a significant impact on several biological processes, including hormone metabolism, cellular proliferation, and cellular transformation and differentiation [20]. In this regard, phytochemicals classified as lignans reveal an extensive range of biological properties, such as antioxidant, antiestrogenic, anti-inflammatory, anticarcinogenic, and anticancer activity [24,25].

Arctiin (Fig. 1) is a lignan, chemically known as (3R,4R)-4-(3,4-dimethoxybenzyl)-3-(3-methoxy-4-(((2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl) tetrahydro-2*H*-pyran-2-yl) oxy) benzyl) dihydrofuran-2(3*H*)-one has been isolated from the leaves, roots, and whole plant of *Arctium lappa* L., *Carthamus tinctoius*, and *Caulis tracherospermi*. In China, this lignan is used for its medicinal properties, resulting from the condensation of pairs of phenylpropane molecules (https://pubchem.ncbi.nlm.nih.gov/compound/100528, accessed on December 02, 2023). Arctiin has a range of pharmacological activities, including anti-oxidative, anti-inflammatory, anticancer, hepatoprotective, antidepressant, and antidiabetic properties [26–28]. Considering the previous discussion and

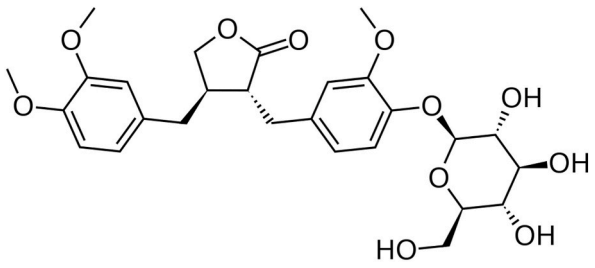

Fig. 1. Chemical structure of arctiin.

due to the extensive array of biological activities and the various preventive and therapeutic possibilities of arctiin against different diseases and forms of cancer. This review focuses on evaluating the anticancer effect of arctiin along with its underlying molecular mechanisms based on existing literature. Additionally, this review discusses the pharmacokinetics and toxicological features of arctiin to provide information on its reliability for developing the compound as an efficacious therapeutic in the treatment of cancer.

2. Methodology

2.1. Literature search stratagem

We included data from 1990 to 2023 in this study, and found relevant references by searching various electronic databases like PubMed, ScienceDirect, Springer Link, Scopus, Wiley Online, Web of Science, ResearchGate, and Google Scholar using the terms "Arctiin," then paired with "Biological sources," "Natural sources," "Botanical sources," "Physicochemical properties," "Chemical features," "PK," "Biopharmaceutics," "Cancer," "Tumor," "Pathophysiology of cancer," "Anticancer activity," "Antiproliferation activity," "Apoptotic effect," "Oxidative stress," "Protective effect," "Cytotoxic activity," "Genotoxic activity," "Carcinogenesis," " Toxicity," "Antitumor activity," "Human cancer," "Biological activities," "Biological evaluation," "Medicinal use," "Pharmacology," "Pharmacological effects," "Pharmacological activities," "*in vivo* studies" or "*in vitro* studies". No language restrictions were imposed. We evaluated the references in-depth, providing information on cancer types, tested doses, effective concentrations, test systems, proposed anticancer action mechanisms, and the overall conclusion.

2.2. Inclusion and exclusion criteria

Inclusion criteria involve a) studies performed *in vitro*, *ex vivo*, or *in vivo* with or without using laboratory animals, including mice, rats, rabbits, and humans, and their derived tissues or cells, b) studies with anticancer activities and botanical sources of arctiin, c) studies with arctiin in combination with other molecules, d) studies with or without hypothesized mechanisms of action, e) studies of the physical and chemical characteristics of arctiin, and f) studies with the biopharmaceutical profiles of arctiin or its preparations. On the other hand, the exclusion criteria involve i) studies that did not meet the inclusion criteria, ii) arctiin, in conjunction with other studies, sheds light on the current issue, iii) papers written in languages other than English, iv) studies do not have complete written content accessible, and v) case reports, letters, editorials, and commentaries.

3. Botanical sources

Medicinal plants have a crucial role in preventing diseases and are incorporated into all existing preventative programs. They are not only used for treating illnesses but also as a potential resource for maintaining good health and well-being [29]. Chemicals from certain plants are a vital source for studies into novel cancer therapies. They may have the capability to be very effective while being less harmful than other compounds [30]. The biologically active compound arctiin has been mostly extracted from the seeds, leaves,

Table 1
Various botanical sources of arctiin.

Name of plants/organisms	Parts	References
Arctium lappa L.	Seeds, Leaves, Fruits and Roots	[26,31,33–37]
Arctium tomentosum	Seeds and roots	[38]
Carthamus tinctoius L.	Seed	[39]
Cousinia concolor	–	[40]
Carduus micropterus ssp.	Aerial parts	[41]
Centaurea sclerolepis	Seeds	[32]
C. Alexandria		
C. melitensis		
C. sphaerocephala		
C. dealbata		
C. nigra		
C. schischkinii		
Forsythia intermedia		
Saussurea heteromalla	Fruits	[42]
Bupleurum fruticosum		
Cnicus benedictus		
Saussurea conica		
Ipomoea cairica,		
Trachelospermum asiaticum		
Wikstroemia viridiflora		
Forsythia suspensa		[43,44]
Centaurea imperialis		
Forsythia viridissima	–	[45]
Saussurea salicifolia	–	[46]
Saussurea medusaas	Aerial part	[47]

roots, and dried ripe fruits of *Arctium lappa* L. plants [31]. The study revealed that it was also found in several *Centaurea* species, including *Centaurea* alexandria, C. melitensis, C. sphaerocephala, *C. dealbata, C. nigra, and C. schischkinii*, as well as *Carduus micropterus* and *Forsythia intermedia*. It has been shown to influence protein biosynthesis, sex hormone metabolism, and steroid biosynthesis [32]. The botanical sources of arctiin are shown in Table 1 **and** Fig. 2.

4. Biopharmaceutical profiles

Natural compounds have a diverse range of possible structural arrangements and are widely recognized as promising prospects for the development of novel medicinal leads. The comprehension and use of pharmacokinetics (PK) are of utmost importance in the exploration and advancement of novel pharmaceutical substances [48]. The function of PK is central in the drug discovery process as it aids in the improvement of the absorption, distribution, metabolism, and excretion (ADME) features of lead compounds. The objective of this optimization is to generate a clinical candidate that demonstrates a concentration-time profile inside the organism that is sufficient to attain the desired effectiveness and safety characteristics [49,50]. The lack of adequate PK data is a common challenge that is often faced throughout the drug development process. In this respect, numerous studies have shown that the predominant variables leading to treatment ineffectiveness may be attributed to inadequate PK and limited bioavailability, together accounting for 40 % of the underlying primary factors [51,52]. Bioavailability refers to the extent and speed at which the active drug component or active moiety from the drug product is absorbed and becomes available at the place where the drug exerts its effects [53,54]. The reasons for the failure of several drug candidates in clinical trials are a lack of considerable PK properties and unacceptable levels of toxicity [55]. Therefore, to identify an optimal dose with therapeutic significance, it is critical to focus on the optimization and characterization of human ADME characteristics, as well as understanding the pharmacokinetic-pharmacodynamic connection [56].

The pharmacokinetic study demonstrated that arctiin was efficiently absorbed and swiftly distributed into a central compartment with high blood flow following oral treatment at dosages of 30, 50, and 70 mg/kg in rats. However, it has poor oral bioavailability, and its elimination from the body was delayed. Additionally, the area under the curve (AUC) did not exhibit a proportionate relationship with the dosage that was provided. The absorption pharmacokinetics of arctiin in rats followed a non-linear pattern within the range of dosages tested. There are differences between male and female rats in terms of the absorption and elimination of arctiin. The half-life

Fig. 2. Pictorial presentation of different botanical sources of arctiin.

($t_{1/2}$), absorption rate constant (K_a), elimination rate constant (k_e), peak concentration (C_{max}), apparent volume (V_d), total body clearance (CL), and AUC of arctiin were considerably greater in female rats compared to males (Table 2) [57,58]. Similarly, the research also indicated that arctiin (at doses of 25–100 mg/kg) had rapid absorption and was quickly distributed throughout all organs in rats after being administered orally. After 30 min, the spleen had the greatest concentration of arctiin among the organs, followed by the heart, lungs, liver, stomach, small intestine, and kidney. In addition, the metabolite exhibited a considerably greater concentration compared to arctiin in the stomach and small intestine of rats. This suggests that the stomach and small intestine, rather than the liver, are the primary organs involved in the metabolism of arctiin [59]. In 2020, Zhang and his research team conducted a study to analyze the metabolites of arctiin in rats. The rats were given a dose of 100 mg/kg. A total of 53 metabolites were discovered and analyzed, with thirty-two detected in plasma, forty in urine, nineteen in bile, twenty in feces, one in the brain, twelve in the liver, and four in the lungs. A total of 38 metabolites were newly reported. The study also discovered that the primary metabolic routes of arctiin in rats included lactone opening, demethylation, and phase II conjugations with sulfate and glucuronide. Furthermore, metabolic patterns of arctiin in rats were first identified by the observation of phase I processes such as hydrolysis, demethylation, dehydroxylation, and dehydrogenation [60]. In another study, rats were administered arctiin at a dosage of 30 mg/kg. The study's findings revealed that arctiin was eliminated at a rate of 19.84 % in urine and 1.80 % in feces. Enterolactone, the primary metabolite, was eliminated in feces at a rate of 35.80 %. Furthermore, arctigenin, which is a known bioactive compound derived from arctiin, was found in small quantities in both urine and feces. Arctigenin may undergo further conversion into enterolactone [61]. It is worth mentioning that the metabolism of arctigenin may vary across various animals. According to Li et al.'s (2017) findings, about 62 %, 3.7 %, 15.7 %, and 25.9 % of the arctigenin substance remained after being exposed to human, monkey, rat, and dog liver microsomes for a duration of 90 min [62]. Additional metabolites detected in SD rats include arctigenin 4-*O*′-sulfate, arctigenic acid-4′-*O*-glucuronide, 4-*O*-demethylarctigenin, and 4-*O*-demethyl-arctigenin-4,4′-*O*-di-glucuronide. Multiple glucuronidation byproducts of arctigenin, such as arctigenin-4′-*O*-glucuronide, were eliminated by bile, indicating the possibility of enterohepatic circulation [63,64]. Fig. 3 shows the metabolism process of arctiin.

5. Anticancer activity of arctiin: underlying molecular mechanisms

New cancer precision medicinal therapies are obtained by using information received from molecular alterations in cancer genes and their related signaling pathways. Currently, there is widespread recognition of the significant involvement of signaling pathways and molecular networks in the execution and regulation of essential cellular processes that facilitate cell survival and proliferation. Consequently, these mechanisms bear substantial responsibility for both the onset and potential therapy of cancer [65]. In the context of cancer, it is frequently observed that two pathways, namely the PI3K/AKT/mTOR signal transduction system and the RAS/MEK pathway, undergo common activation or mutation [66]. In addition, CDK4/6 inhibitors have shown substantial progress in the field of cancer therapy by effectively blocking the activation of CDK4/6 across many signaling pathways [67].

Several studies suggest that arctiin, a medicinal substance, might combat cancer through various mechanisms. It appears to

Table 2
Summary of pharmacokinetic parameters of arctiin in different preclinical studies.

Species	Dose (mg/kg) (oral)		Pharmacokinetics parameters							References
			$t_{1/2}$	K_a	K_e	C_{max}	V_d	AUC	CL	
SD rats	Male	30	59.21 ± 6.218 min	0.06 ± 0.005 1/min	0.02 ± 0.003 1/min	0.78 ± 0.030 mg/L	5.83 ± 0.953 L/kg	98.77 ± 9.780 mg min/L	0.07 ± 0.008 L/min/kg	[57]
		50	63.70 ± 7.372 min	0.07 ± 0.009 1/min	0.05 ± 0.009 1/min	1.16 ± 0.160 mg/L	15.70 ± 3.260 L/kg	111.17 ± 13.074 mg min/L	0.15 ± 0.024 L/min/kg	
		70	62.79 ± 4.321 min	0.10 ± 0.006 1/min	0.04 ± 0.006 1/min	1.88 ± 0.050 mg/L	24.69 ± 3.140 L/kg	130.77 ± 6.728 mg min/L	0.26 ± 0.034 L/min/kg	
	Female	30	58.85 ± 5.010 min	0.13 ± 0.013 1/min	0.02 ± 0.003 1/min	0.85 ± 0.070 mg/L	16.08 ± 2.283 L/kg	112.25 ± 10.820 mg min/L	0.13 ± 0.026 L/min/kg	
		50	69.99 ± 8.733 min	0.12 ± 0.014 1/min	0.06 ± 0.010 1/min	4.10 ± 0.594 mg/L	14.32 ± 2.260 L/kg	134.29 ± 21.313 mg min/L	0.29 ± 0.079 L/min/kg	
		70	89.97 ± 11.959 min	0.14 ± 0.004 1/min	0.07 ± 0.011 1/min	4.79 ± 1.070 mg/L	11.19 ± 1.830 L/kg	168.08 ± 23.249 mg min/L	0.41 ± 0.062 L/min/kg	
SD rats	Male	25	2.32 ± 0.22 h	–	–	0.70 ± 0.15 mg/L	–	3.32 ± 1.09 mg h/L	16.3 ± 5.5 L/h/kg	[59]
		50	4.70 ± 1.99 h	–	–	1.59 ± 0.20 mg/L	–	9.34 ± 1.09 mg h/L	2.70 ± 0.32 L/h/kg	
		100	5.18 ± 1.35 h	–	–	2.50 ± 1.26 mg/L	–	7.07 ± 1.44 mg h/L	14.6 ± 3.0 L/h/kg	

min: minutes; hr: hour; $t_{1/2}$: Half-life; K_a: Absorption rate constant; k_e: Elimination rate constant C_{max}: Peak concentration; V_d: Apparent volume; AUC: Area under curve; CL: Total body clearance.

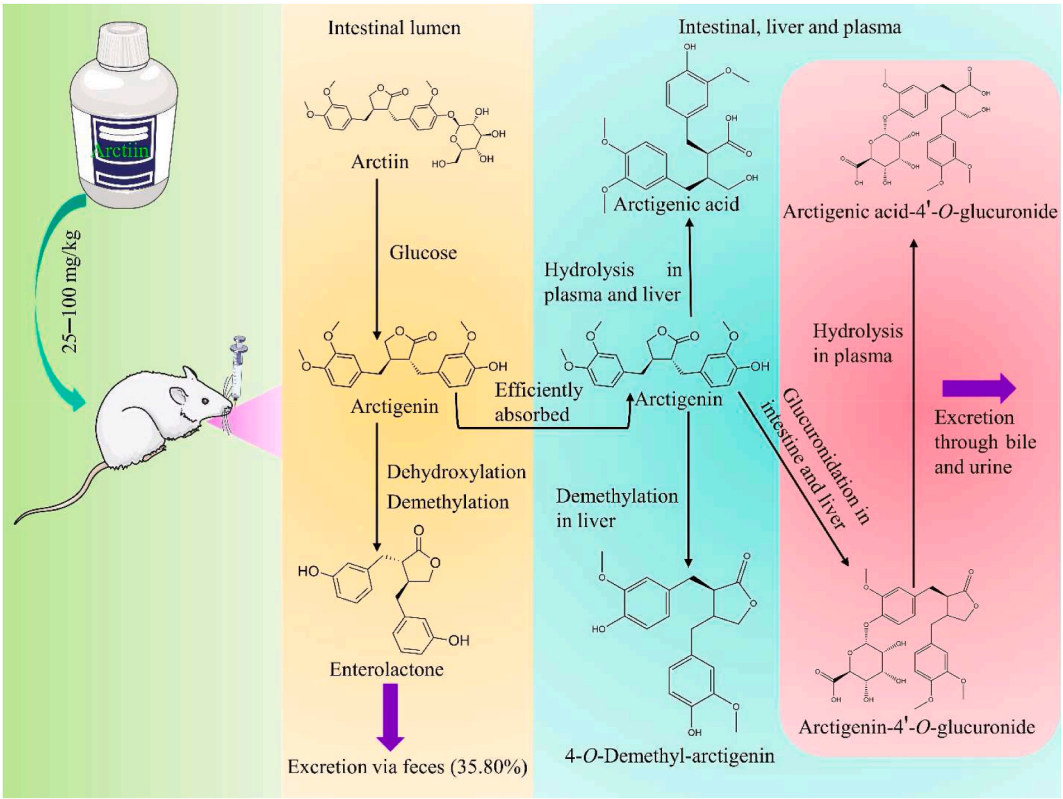

Fig. 3. The possible metabolic pathway of arctiin in a preclinical test system.

interfere with oxidative stress and mitochondrial dysfunction, disrupt the cell cycle, inhibit metastasis, induce apoptosis, curb cell proliferation, and diminish carcinogenesis in experimental models [27,34,68,69]. Molecular anticancer mechanisms of arctiin involved in various cancers are reported in different database reports (Table 3). Depicted in Fig. 4 are the possible anticancer mechanisms of arctiin in different types of cancer.

5.1. *Alleviation of the mitochondrial membrane potential*

Mitochondria are intracellular organelles that play a crucial role in cellular function through the metabolism of nutrients and the production of adenosine triphosphate (ATP), the primary energy currency. They are also involved in several processes, including energy metabolism, the generation of free radicals, calcium homeostasis, and the regulation of cell survival and death [70,71]. Targeting this distinct cellular function might offer a less cytotoxic alternative compared to conventional chemotherapeutic medicines that indiscriminately destroy quickly dividing tumor cells [72]. A recent study has demonstrated that arctiin exhibits possible anticancer properties that are effective in the treatment of myeloma cancer. Arctiin (10 μM) suppresses myeloma cancer cells (U266) proliferation and mediates apoptosis via the alleviation of mitochondrial membrane potential [34].

5.2. *Cytotoxicity and toxicity*

The cytotoxicity test is essential for evaluating the potential of an anticancer agent. It provides valuable insights into whether the agent is suitable for cancer treatment [73]. In this context, it is essential to consider assessments of cytotoxic effects that are dependent on both time and concentration [74]. Cytotoxicity, or the process of destroying cells, is the primary mechanism of action of chemotherapeutic medicines. The purpose of these pharmaceutical agents is to specifically and preferentially target malignant cells that have a heightened propensity for cellular division, with the ultimate objective of inhibiting the development and advancement of tumors [75]. Therefore, the presence of toxicity in a chemical significantly increases the potential for using the substance as a chemotherapeutic agent [76].

Several studies indicated that arctiin has substantial cytotoxic properties against diverse cancer cell lines. In this regard, arctiin (10 μM) showed few cytotoxic actions against human myeloma cancer cells (U266) [34]. Findings by Su et al. (2015) showed that arctiin exhibits cytotoxicity to CEM/ADR 5000 and CaCo2 cancer cell lines with IC_{50} values of 350 and >5000 μM, respectively [77]. Another study revealed that arctiin at concentrations of 50–200 μg/mL displayed a moderate cytotoxic effect in human gastric adenocarcinoma cells (AGS) [46]. Moreover, cancer cell viability was remarkably reduced by arctiin (0.5 μM) treatment in DLD1 cancer cells [78].

Table 3
Anticancer activity of arctiin involved in various cancers obtained from different preclinical tests.

Type of Cancer	Experimental model/ cell line	Tested Concentrations	Efficacy, IC50 (exposure time)	Anticancer Effects and Mechanisms	References
Cervical cancer	HeLa, and SiHa, *in vitro*	10–80 μM	–	↓Migration and invasion, ↓S100A4 protein expression, ↓PI3K/AKT pathway	[27]
Myeloma cancer	U266, *in vitro*	10 μM	–	↓Proliferation, ↓Cell cycle (G2/M phase), ↓Mitochondrial membrane potential, ↑Apoptosis, ↑PARP cleavage, ↑Caspase-3, ↓STAT3 phosphorylation, ↓Src phosphorylation, ↓JAK1/2, ↑ PTPε expression, ↓Cyclin D1 and survivin expression, ↑Cytotoxicity	[34]
–	MCF-7, *in vitro*	10 μM	–	↓Proliferation	[33]
–	MCF-7, *in vitro*	–	–	↓Cyclin D1, ↓Proliferation	[68]
–	Sprague-Dawley (SD) rats, *in vivo*	–	–	↓Carcinogenesis	[113]
Prostate cancer	transgenic rats, *in vivo*	–	–	↓Carcinogenesis	[26]
Colon cancer	SW480, *in vitro*	100–400 μM	220.7 μM (48h)	↓Proliferation	[94]
–	Male F344 rats, *in vivo*	1.5 ppm	–	↓Carcinogenesis, ↓Foci development	[114]
–	CEM/ADR 5000 and CaCo2, *in vitro*	–	350 and > 5000 μM	↑Cytotoxicity	[77]
Gastric cancer	AGS, *in vitro*	50–200 μg/mL	–	↑Cytotoxicity, ↓Proliferation	[46]
–	Sprague-Dawley (SD) rats, *in vivo*	40–1000 ppm	–	↓Tumor development	[39]
Endothelial cancer	HRCEC, *in vitro*	0.05–2 μg/mL	–	↑ROCK1, ↑PTEN, ↓PI3K, ↓AKT, ↓VEGF, ↓Proliferation, ↓Cell cycle (G2/M), ↓CDK4, ↓CDK2, ↓Cyclin D1	[69]
–	Sprague Dawley rats, *in vivo*	30–100 mg/kg	–	↓Inflammation, ↓Fibrosis, ↓Tumor migration, ↓TLR4, ↓NLRP3, ↓STAT3, ↓TGF-β, ↓VEGF, ↓Cyclin D1	[106]
–	HL-60, *in vitro*	–	114 μg/mL	↓Proliferation	[36]
–	DLD1, *in vitro*	0.5 μM	–	↓Cell viability	[78]
–	HEK, *in vitro*	–	10.8 μg/mL	↑Cytotoxicity	[40]
–	ICR and SENCAR (6-weeks-old) mice, *in vivo*	–	–	↓Skin carcinogenesis, ↓Skin papilloma formation	[47]
–	HepG2, *in vitro*		2.60 μg/mL	↑Cytotoxicity	[79]

Arrows (↑ and ↓) show an increase and decrease in the obtained variables. PI3K: Phosphoinositide 3-kinase; AKT: Protein kinase B; PARP: Poly (ADP-ribose) polymerase; Src: Proto-oncogene tyrosine-protein kinase; JAK1: Janus kinase 1; JAK1,2: Janus kinase 2; PTP: Protein tyrosine phosphatase; STAT3: Signal transducer and activator of transcription 3; ROCK1: Protein serine/threonine kinase; PTEN: Phosphatase and Tensin Homolog deleted on Chromosome 10; CDK 2,4: Cyclin-dependent kinase 2,4; NLRP3: Nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3; TLR4: Toll-like receptor 4; VEGF: Vascular endothelial growth factor; TGF-β: Transforming growth factor-beta.

Similarly, arctiin exhibited a potent cytotoxic effect on HEK cancer cells, with an IC_{50} value of 10.8 μg/mL [40]. Finally, the lignan compound arctiin showed cytotoxicity in cancer cells (HepG2) with an IC_{50} value of 2.60 μg/mL [79]. Further toxicological research findings showed that arctiin did not exhibit any obvious harmful effects on shrimp larvae (LC_{50} > 1000 μg/mL) in different concentrations (48–1000 μg/mL) [32]. Another study demonstrated that arctiin exhibits considerable toxicity in a brine shrimp lethality assay with an LD_{50} of 98.0 μg/mL [80,81]. However, at a higher dose of 10 μM, arctiin showed moderate toxicity in the raw 264.7 cell line, but at a dose of 1 μM, it did not show any cytotoxic effect [82]. In summary, it is well acknowledged that therapeutic dosages of anticancer drugs might lead to the occurrence of harmful side effects due to their cytotoxic nature and limited ability to distinguish between target cells and healthy cells [83]. In contrast, arctiin exerts significant anticancer properties with less toxic effects at low doses. Therefore, it is crucial to carry out thorough studies to conclusively determine the toxicity levels or maximum tolerable limits.

5.3. Cell cycle arrest

The process through which cells undergo multiplication and generate two cells from one mother cell is referred to as the cell cycle [84]. The cell cycle is a series of carefully regulated stages. In the event of any disruptions or genetic mutations occurring during a particular phase, the cell's progression to subsequent phases of the cycle is impeded [85]. At present, treatment of cancer entails the regulation of gene expression and modulation of intracellular enzymes, proteins, and signaling molecules to govern the cell cycle [86–88]. Therefore, cell cycle regulators are seen as interesting targets for developing cancer therapeutics [89]. Recent research findings showed that arctiin (10 μM) significantly inhibits the cell cycle at the G2/M phase through suppression of cyclin D1 and surviving protein expression in myeloma cancer (U266) cells [34]. Similarly, arctiin inhibited STAT3 phosphorylation, Src phosphorylation, and JAK1/2 signaling, as well as increased PARP cleavage, caspase-3, and PTPε protein expression. In addition, a study by Zhou et al. (2020) revealed that arctiin (0.05–2 μg/mL) inhibits the cell cycle at the G_0/G1 phase in HG-induced HRCECs through the suppression of cyclin D1 CDK2, and CDK4 [69].

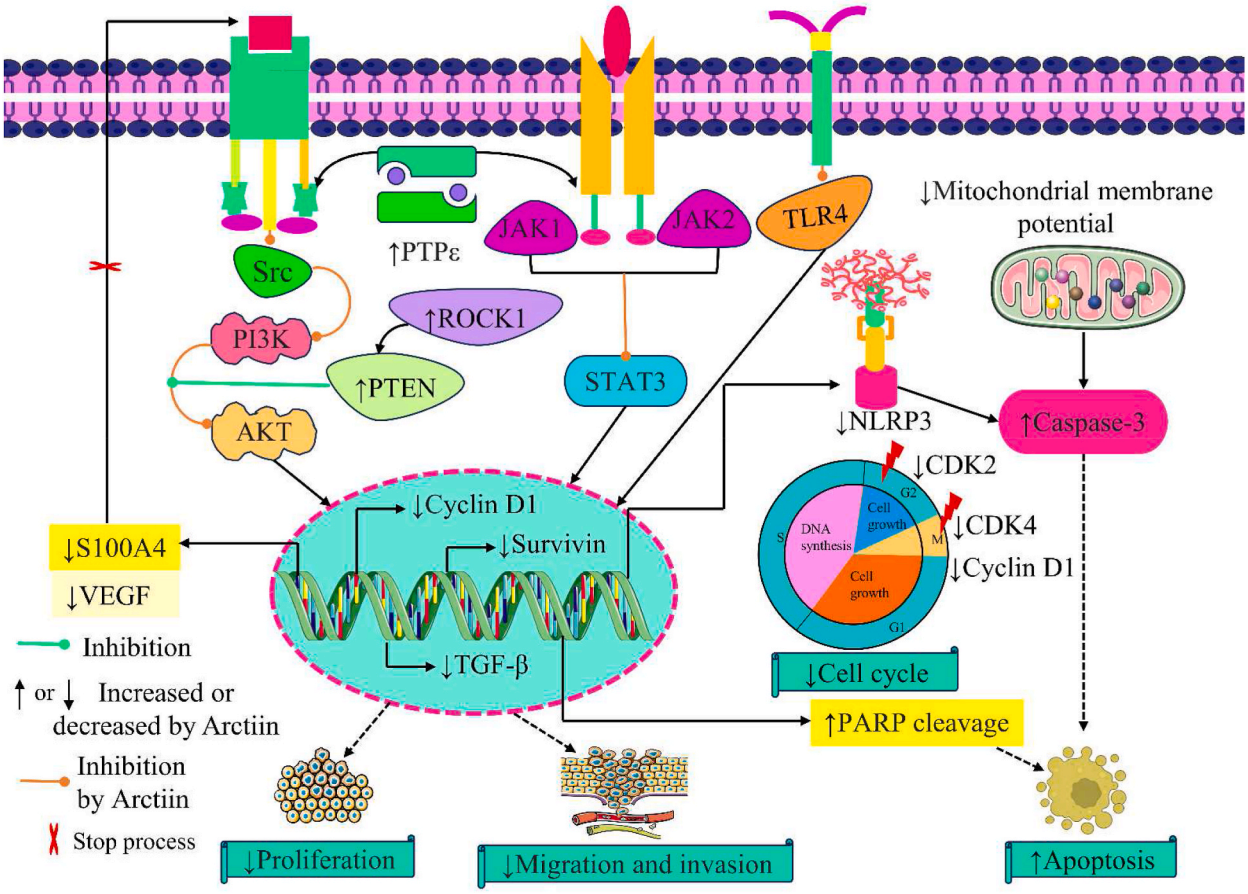

Fig. 4. The possible mechanism of arctiin in different types of cancers. [PI3K: phosphoinositide 3-kinase; AKT: Protein kinase B; PARP: Poly (ADP-ribose) polymerase; Src: Proto-oncogene tyrosine-protein kinase; JAK1: Janus kinase 1; JAK1,2: Janus kinase 2; PTP: protein tyrosine phosphatase; STAT3: signal transducer and activator of transcription 3; ROCK1: protein serine/threonine kinase; PTEN: Phosphatase and Tensin Homolog deleted on Chromosome 10; CDK 2,4: Cyclin-dependent kinase 2,4; NLRP3: Nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3; TLR4: Toll-like receptor 4; VEGF: Vascular endothelial growth factor; TGF-β: Transforming growth factor-beta].

5.4. Anti-proliferative effect

The process of cancer development and advancement is characterized by the excessive growth of abnormal cells, a phenomenon described by alterations in the expression or functionality of proteins related to the cell cycle [90]. Additionally, consistent activation of multiple signaling pathways impels cell development. A crucial factor in the emergence and spread of cancer is proliferation. Human malignancies frequently are active in the PI3K/Akt/mTOR signaling pathway, which is important in cell growth, survival, and proliferation [91]. Additionally, the JAK/STAT pathway plays a crucial role in regulating the growth and viability of immune system cells. Nevertheless, the excessive activation of JAK/STAT proteins, together with the decrease in a diverse suppressor of cytokine signaling (SOCS) proteins, is linked to the proliferation, advancement, spread, and survival of distinct forms of cancer cells [92,93]. Therefore, inhibition of these signaling pathways is a good option for cancer treatment.

The lignan arctiin (at concentrations of 10 μM) has shown a potent anti-proliferative effect on myeloma cancer cells (U266) through the inhibition of STAT3 phosphorylation, Src phosphorylation, and JAK1/2 signaling, as well as cyclin D1 and survivin expression. Additionally, arctiin elevated PTPε expression, PARP cleavage, and caspase-3 activity [34]. Xie and coworkers showed that arctiin inhibits cell proliferation in MCF-7 cancer cells at a 10 μM concentration [33]. Likewise, arctiin suppresses cell growth through the alleviation of cyclin D1 protein expression [68]. Another investigation indicated that arctiin (100–400 μM) impedes the growth of colon cancer cells (SW480) with an IC_{50} value of 220.7 μM at the 48-h exposure time [94]. Furthermore, Kang and colleagues demonstrated that arctiin diminishes the proliferation of human gastric cancer cells (AGS cells) at concentrations of 50–200 μg/ml [46]. Similarly, arctiin (0.05–2 μg/mL) inhibited the proliferation of endothelial cancer cells (HRCEC) through the up-regulation of ROCK1 and PTEN activity and the downregulation of PI3K, AKT, and VEGF signaling [69]. Finally, findings from another investigation indicated that arctiin suppresses the proliferation of HL-60 cancer cells with an IC_{50} value of 114 μg/mL [36]. Overall, the findings showed that arctiin exhibits anti-proliferative activity in different cancer cells through the VEGF, JAK/STAT, and PI3K/AKT signaling pathways.

5.5. Apoptotic effect

Apoptosis is a biological process of planned cell death that takes place inside the human body. It is characterized by a series of internal and extrinsic processes that result in distinct cellular morphological alterations and eventual death [95,96]. Caspases are a class of specialized proteolytic enzymes responsible for the induction and execution of apoptosis [97]. Similarly, the nuclear protein poly (ADP-ribose) polymerase 1 (PARP1) is a key component of cellular processes; cleavage of PARP1 results in its functional impairment, hence inhibiting the process of DNA repair [98,99]. One of the notable characteristics of apoptosis is the enzymatic cleavage of PARP1 by caspases [100]. On the other hand, blocking JAK/STAT signaling promotes apoptosis in a variety of malignancies and inhibits the development of cancer cells [101]. Published research indicates that arctiin can induce apoptosis in preclinical cancer studies. Research findings showed that arctiin (10 μM) elevates the apoptotic process through the up-regulation of PARP cleavage and caspase-3 activity. Additionally, arctiin down-regulated STAT3 phosphorylation, Src phosphorylation, and JAK1/2 signaling, together with decreased Cyclin D1 and survivin protein expression in myeloma cancer cells (U266) [34].

5.6. Inhibition of cancer cell migration and invasion

Metastatic illness is the primary cause of death for cancer patients, and it is mostly attributed to the migration and invasion of cancer cells. Several different processes, such as amoeboid cell migration, mesenchymal cell migration, and collective cell migration, can be used by cancer cells to spread and move [102]. VEGF, also known as vascular endothelial growth factor, is a signaling molecule that is secreted by epithelial cells and plays a crucial role in promoting cell proliferation [103]. Similarly, research has revealed that the NLRP3 inflammasome has a role in promoting the growth and spread of breast cancer by triggering the release of pro-inflammatory substances [104]. Additionally, the activation of the PI3K-AKT signaling pathway enhances the motility and invasion of prostate cancer cells [105]. So, impeding the action of this macromolecule is the primary option for cancer drug discovery and development. Recent research findings suggest that arctiin impedes cell migration and invasion in different cancer cells. In this context, Lee et al. (2022) showed that arctiin (10–80 μM) suppresses cell migration and invasion by downregulating the PI3K/AKT signaling pathway and diminishing the expression of the S100A4 protein in cervical cancer cells (HeLa and SiHa) [27]. Another study showed that arctiin (30–100 mg/kg) suppresses inflammation, fibrosis, and tumor migration through TLR4, NLRP3, and TGF-β expression. Additionally, it suppressed STAT3 and VEGF signaling and decreased Cyclin D1 protein expression [106]. Therefore, the findings of these studies demonstrated that arctiin inhibits cancer cell migration and invasion via suppression of the VEGF, STAT3, and PI3K/AKT signaling pathways.

5.7. Miscellaneous effects

Carcinogenesis, alternatively referred to as oncogenesis or tumorigenesis, refers to the biological process through which the development of cancer occurs, involving the conversion of normal cells into cancer cells. The process is distinguished by alterations occurring at the cellular, genomic, and epigenetic tiers, as well as aberrant cell proliferation [107]. In the field of cancer treatment, there are a variety of drugs and radiation aimed at preventing cancer [108,109]. These drugs and radiation can modify the normal functioning of healthy cells by altering oncogenes and proto-oncogenes, thereby initiating the process of carcinogenesis [110–112]. This is why it is imperative to identify substances that can inhibit the operation of malignant cells without adversely affecting the normal functioning of healthy cells, along with protective effects on radiation treatment.

Several researchers have demonstrated that arctiin can reduce carcinogenic properties in preclinical testing systems. In this context, Hirose et al. (2000) showed that arctiin suppresses carcinogenesis in rats [113]. Similarly, arctiin reduces carcinogenesis in prostate cancer in transgenic rats [26]. Additionally, arctiin (1.5 ppm) impedes the carcinogenic properties and foci development in male F344 rats [114]. Further, Hasumura et al. (2007) demonstrated that arctiin (40–1000 ppm) suppresses tumor development in Sprague-Dawley (SD) rats [39]. Finally, the lignan compound arctiin reduced skin carcinogenesis and skin papilloma formation in ICR and SENCAR (6-week-old) mice [47]. In summary, the carcinogenic effect is mitigated by the treatment of arctiin at different concentrations. Shown in Table 3 are the anticancer activity of arctiin in different types of cancer.

6. Pharmacological relevance

The lignan compound arctiin has been used to treat or manage diseases, alleviate symptoms, or improve health outcomes. Arctiin (25–100 mg/kg) improves depression by suppressing the activation of microglia and inflammation through the HMGB1/TLR4 and TNF-α/TNFR1 signaling pathways [37]. Arctiin, administered at a dosage of 15–60 mg/kg, protects the rat heart after ischemia or reperfusion injury. This protection is accompanied by a reduction in the levels of necroptosis-associated proteins (RIPK1/p-RIPK1, RIPK3/p-RIPK3, and MLKL/p-MLKL). Additionally, arctiin helps to alleviate mitochondrial dysfunctions [35]. Another study showed that arctiin (80 mg/kg) protects against heart hypertrophy by blocking the MAPKs and AKT signaling pathways [115]. Furthermore, arctiin improves toxoplasma gondii HSP70-induced acute liver injury caused by allergies by suppressing the activation of the TLR4/mitogen-activated protein kinase/nuclear factor-kappa B signaling pathway, therefore, preventing excessive synthesis of cPLA2, PAF, and interferon-γ [116]. Another study found that arctiin (500 mg/kg) has the potential to reduce TP-induced liver damage by activating the Nrf2 pathway [69]. In this context, arctiin-encapsulated DSPE-PEG bubble-like nanoparticles (40 μL) exhibited a protective effect on mice by preventing pulmonary fibrosis generated by bleomycin while not causing notable harm to the heart, liver, spleen, or kidney. In addition, it suppressed the aging of alveolar epithelial type 2 cells and prevented lung fibrosis by suppressing the

p38, p53, and p21 signaling pathways [117].

Likewise, arctiin, when administered at a dosage of 10–40 mg/kg, effectively suppressed the phosphorylation of PI3K/Akt and the activation of NF-κB produced by LPS. This caused the inhibition of proinflammatory cytokines and protected the lungs [118]. Treatment with Arctiin at a dosage of 100 mg/kg caused increased levels of motilin and brain-derived neurotrophic factor, as well as decreased levels of nitric oxide and injury to interstitial cells of Cajal in the colon of mice with functional constipation [119]. Arctiin, at a dosage of 500 mg/kg, mitigated the renal tissue injuries caused by triptolide. Concurrently, the compound effectively suppressed the harmful effects of triptolide on HK-2 cells and enhanced their survival rate [120]. Findings also found that arctiin inhibits the inflammatory response caused by the H9N2 avian influenza virus by activating the Nrf2/HO-1 signaling pathway [121]. In addition, several studies revealed that arctiin has antidiabetic [28], anti-obesity [122], antiasthmatic [123], antiarthritic [124], and has anti-inflammatory activity [82,106,125]. In summary, arctiin has a diverse range of applications in pharmacology. In addition, treatment of laboratory animals with arctiin did not causet any potential toxicity like neurotoxicity, cardiotoxicity, hepatotoxicity, and nephrotoxicity. So, it is relatively safe and effective for the management of disease and disorder.

Arctiin exhibits greater anticancer activity at concentrations over 100 μM. It is possible to develop a molecule with cytotoxicity greater than 100 μM as an anticancer medication. A significant number of well-established chemotherapy medicines fall within this spectrum. For example, certain studies indicated that 5-fluorouracil, a commonly used chemotherapy agent, demonstrates lethal effects within more than 200 μM for specific types of cancer cells [126,127]. Research is being conducted on natural substances for the treatment of cancer. In this respect, plants and other species show potential for providing valuable clues, as certain natural extracts have displayed cytotoxicity levels over 100 μM in cancer cell lines [128,129]. Nevertheless, attaining a high level of cytotoxicity is but one component of a triumphant anticancer medication. Additional criteria that should be taken into account include (1) selectivity (cytotoxicity on specific cells), (2) mechanism of action (how it suppresses cancer); and (3) pharmacokinetics and safety [130]. Besides, arctiin has poor oral bioavailability. To overcome this problem, research on their derivatives, changing the administration site, or improving the formulation of the arctiin is required. So, it is possible that arctiin can be developed as an anti-growth chemical for cancer treatment.

7. Clinical evidence

The primary dietary sources of lignans, including whole grains, fruits, and vegetables, are foods often linked to reducing the risk of cardiovascular diseases and cancer [131]. Lignans, which have a similar structure to naturally occurring sex steroid hormones, might potentially modify hormone metabolism in the body and hence protect against the risk of developing cancer [132]. Arctiin functions as a marker in the quality assurance of certain exclusive Chinese medications. Most of these items are intended for the treatment of the common flu, cold, and associated symptoms. They include several kinds of Yinqiaojiedu decoction, Fengreganmao granules, and Lingyang ganmao decoction [125]. There is a lack of clinical data supporting the use of the lignan compound arctiin as an anticancer drug. However, clinical studies showed that dietary plant lignan reduces breast cancer in premenopausal women through the reduction of Ki-67 biomarker and c-erbB2 expression as well as an increase in apoptosis [133,134]. Similarly, the lignan derived from flaxseed effectively inhibited cell division by decreasing the level of Ki-67 in the benign breast tissue of premenopausal women, who have a higher chance of developing breast cancer [135]. In a prior study, consuming lignan was linked to a decreased chance of developing breast cancer [136,137]. Further, the growth of prostate cancer cells may be impeded by lignan produced from flaxseed via pathways related to VEGF [138]. Additionally, two meta-analyses of studies examining the relationship between dietary lignan consumption and postmenopausal breast cancer risk found that a higher intake of lignans was linked to a small but statistically significant decrease in the chance of developing breast cancer [139,140]. Since then, several *in vivo* and *in vitro* studies have revealed that the lignan compound arctiin has an anticancer property. So, it requires a clinical study of arctiin as an anticancer agent.

8. Conclusions

In conclusion, despite the substantial advancements in the field of cancer therapy, this severe disease continues to be a major cause of mortality, resulting in a huge number of deaths each year. Chemotherapy is a promising strategy for treating cancer, and natural products, especially arctiin, hold promise as potential reservoirs of lead molecules with anticancer properties. Findings from this review indicate that arctiin shows significant anticancer properties against a range of cancer types, including myeloma, colon, prostate, and cervical cancer. The observed anti-tumor effects encompass a variety of mechanisms, such as cytotoxicity, apoptotic cell death, cell cycle arrest, inhibition of migration, and proliferation. Among the numerous pathways investigated, arctiin was shown to be more potent in terms of the PI3K/AKT and the JAK/STAT signaling pathways. This enhanced interaction capability implies that arctiin has a greater potential for tumor treatment. However, the oral bioavailability of arctiin is quite poor, suggesting that its effectiveness when administered orally is limited. Therefore, it may be necessary to explore other methods of administration as well as improve the formulation. This includes the use of nanosuspensions, solid lipid nanoparticles, polymeric nano- and microparticles, phytosomes, liposomes, niosomes, and microemulsions. Further research is required to thoroughly clarify the anticancer effect of arctiin across many cancer classifications, despite the promising results seen so far. Considering any possible limitations, findings of this research indicate that arctiin has the fundamental characteristics necessary to serve as a promising lead molecule in the development of novel and effective anticancer drugs.

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Data availability statement

The data presented in this study are available on request from the corresponding author.

CRediT authorship contribution statement

Raihan Chowdhury: Writing – original draft, Methodology, Conceptualization. **Md Shimul Bhuia:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Polrat Wilairatana:** Writing – review & editing, Data curation. **Meher Afroz:** Writing – original draft. **Rubel Hasan:** Formal analysis, Data curation. **Jannatul Ferdous:** Writing – original draft, Methodology. **Asraful Islam Rakib:** Writing – original draft. **Salehin Sheikh:** Writing – original draft, Data curation. **Mohammad S. Mubarak:** Writing – review & editing, Visualization, Validation, Supervision, Project administration. **Muhammad Torequl Islam:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

We declare that this work has not been published previously and is not under consideration for publication elsewhere and that all authors approve its publication. If accepted, it will not be published elsewhere in the same form, in English or any other language, including electronically without the written consent of the copyright holder.

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