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SCORPION VENOM AND ITS COMPONENTS AS NEW PHARMACEUTICAL APPROACH TO CANCER TREATMENT, A SYSTEMATIC REVIEW

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ABSTRACT: The use of scorpion venom has a very old history in traditional medicine for thousands years ago in China, India and Africa worldwide. The inhibition of cancer progression and induce apoptosis have shown in an increasing number *in-vitro* and *in-vivo* studies. We accomplished this systematic review to evaluate the performance of scorpion venom and its components in the growth inhibition of cancer cell lines. To provide a full data for future researches, the *in-vitro* and *in-vivo* studies were adopted in this research. The literature search for the published articles from January 1st, 1968 to January 1th, 2018 was done in PubMed, ISI Web of Science, Scopus, and Science Direct. All the articles were independently screened by applying some predefined criteria by two reviewers in three consecutive steps. We identified 53 eligible studies from among 1,209 studies. So far, scorpion venom and its components have been discovered to inhibit the growth of 38 various types of cancer cell lines. This was the first systematic review includes some tables that provided some valuable information to the reader on the therapeutic properties of scorpion venom and its components in the sphere of cancer treatment. We found some studies showing that these agents have been able to inhibit the growth of cancer cell lines, while having no effects on the normal cells using the same doses. The findings of this research strongly reinforced the hypothesis that these agents provide a new efficient approach to cancer treatment.

INTRODUCTION: Scorpions have lived anywhere on the earth since over 400 million years ago. More than 1,500 species have been reported to exist so far [1]. Due to developing such symptoms as pain, swelling, hypertension, cardiac arrhythmia, and other systemic complexities caused by stinging and subsequent envenomation, they have spread a negative reputation among people [2, 3].

Nevertheless, the Chinese, Indian, and African traditional medicines have made a use of scorpions and their venoms for thousands of years [4]. The direct and indirect functions of these cytotoxic agents broadly involve the ion channels of cell membranes and activation of cellular metabolic pathways, perhaps with the help of secondary messengers, respectively [5]. Yet, besides their neurotoxic activities, some have antitumor

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properties. Under *in-vitro* or *in-vivo* conditions, cell cycle arrest and apoptosis induction, as well as inhibition of cancer proliferation and metastasis have been demonstrated to be caused by some purified peptides and proteins with the help of crude scorpion venom in an increasing number of pre-clinical and experimental researches [3]. In this regard, new potent anticancer drugs with fewer side effects have been continuously searched by oncologists since some drugs have been found to leave adverse effects on the non-involved vital organs like nervous system, heart, liver, bladder, kidney, and lungs [6]. This approach has led to choosing scorpion venom and its components as good candidates for cancer treatment.

Although there were some review articles collecting some studies about the anti-cancer properties of scorpion venom, there was no study, in which the data had been fully extracted. Thus, we performed a systematic review includes some tables that provide valuable information to the reader.

METHODS:

1.1. The Criteria for Including Studies: Since the purpose of this systematic review was to evaluate a natural venom performance in the treatment of cancer cell lines, we designed some criteria for the selection of studies to help us answer our study question. We selected the studies, in which cancer cell lines had been exclusively used for showing the modulatory effects of scorpion venom on the mentioned cell growth. There were many studies using cell lines because of their immortalities and highly growth rate properties. In such studies, the main objective had been to study the mechanisms of scorpion venom effects, especially on ion channel blockers. Therefore, we excluded these studies regarding the titles and abstracts.

1.2. Study Selection: This systematic review was performed following the recommendations outlined in the PRISMA guidelines. Here include at least the web address (www.prisma-statement.org). After searching in PubMed, ISI Web of Science, Scopus and Science Direct online databases, we manually searched for the reference lists of all the relevant articles for additional studies. The duplicated studies were removed and the first reviewer (M.R) excluded those articles that did not meet the eligibility criteria with regard to the titles and abstracts. The full texts were read when necessary. If the first reviewer could not decide on excluding the article, the second reviewer (M.S) was asked for consultation until both reached a consensus. Furthermore, a single reviewer collected the relevant data from the included articles for the study.

1.3. Data Extraction: To prepare a full extraction from the included studies, we divided the data extraction into two separate parts including the *in - vitro* and *in-vivo* studies. For the *in-vitro* studies, we extracted the author(s), year, cell line, organism, disease, scorpion species, crude venom/component, IC_{50}, and the results (positive or negative).

2. RESULTS:

2.1. Search Results: Our search in PubMed, ISI Web of Science, Scopus, and Science Direct databases provided a total of 1,209 citations. We manually searched the reference lists of all the related articles for additional studies and found 20 studies. After adjusting for the duplicates, 334 articles were remained. Two hundred and fourteen studies were discarded because after reviewing their titles and abstracts, it appeared that the papers did not clearly meet the criteria. The full texts of the remaining 94 citations were examined in detail. Finally, 53 studies were identified to be included in the study. **Fig. 1** exhibits the search and study selection processes provided in a flow chart of this systematic review.

Data Extraction: After including the eligible studies based on the goal of this research, we separately extracted the data from the *in-vitro* and *in vivo* studies. The number of *in-vivo* studies was less than that of the *in-vitro* studies (13 *vs.* 40 studies). The results revealed that this natural venom and its components had inhibited the growth of 38 various types of cancer cell lines. The *in-vitro* and *in-vivo* successes in the growth inhibition were 92% and 100%, respectively. Also, the cell lines of 28 various types of the disease were found to have been defeated by these agents. The venoms of 18 species had been used in the treatment in the two forms of crude venom and component. Their summaries of numerical information are displayed in **Tables 1** and **2**, respectively.

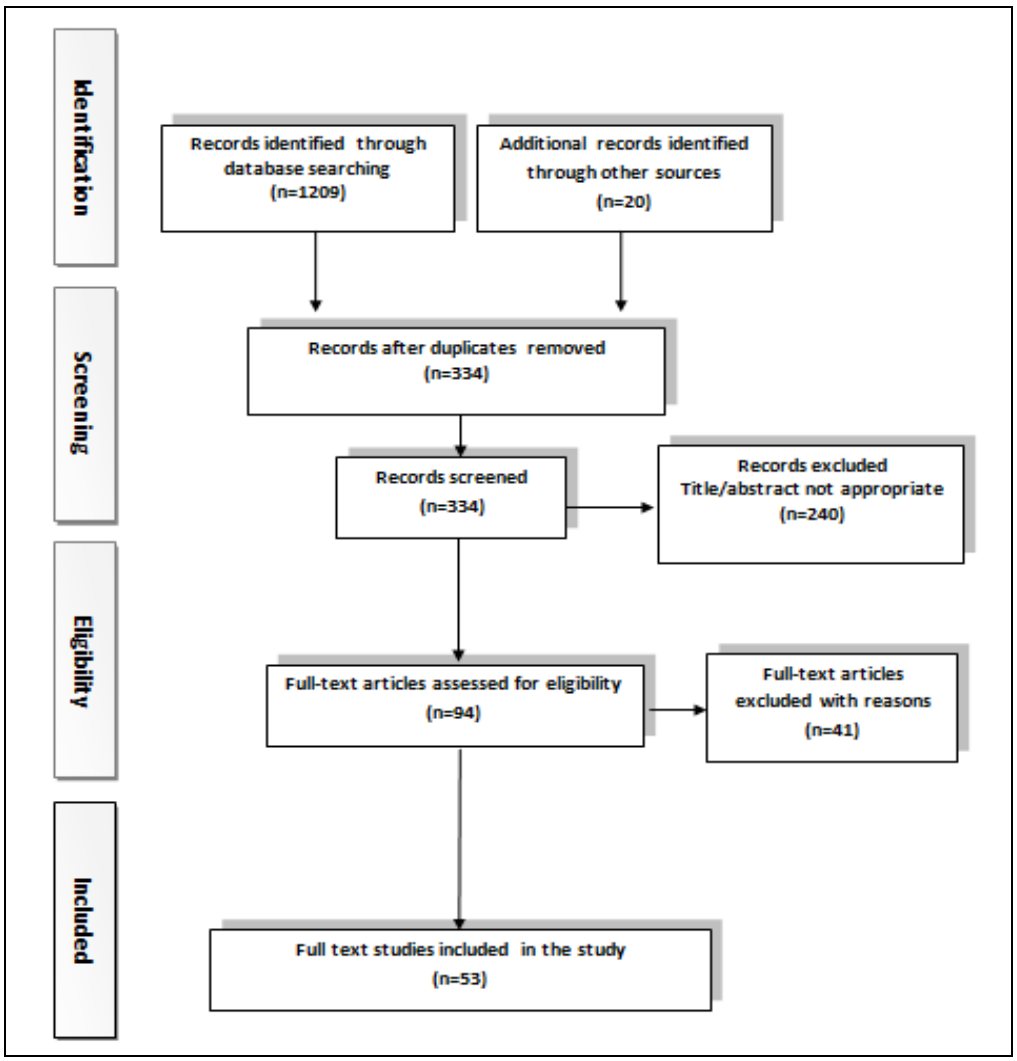

FIG. 1: PRISMA DIAGRAM OF SCREENING PROCESS AND STUDY SELECTION

TABLE 1: SUMMARY OF NUMERICAL INFORMATION IN *VITRO* STUDIES

Cell lines	Organism			Disease	Scorpion species	Crude venom / component		Result	
	Human	Rat	Mouse			Component	Crude	Positive	Negative
38	35	2	1	28	18	29	27	78	7

TABLE 2: SUMMARY OF NUMERICAL INFORMATION IN *VIVO* STUDIES

Cell lines	Organism			Disease	Crude venom / component		Result	
	Human	Rat	Mouse		component	Crude	Positive	Negative
8	4	1	3	6	11	1	16	0

The *in-vitro* and *in-vivo* results of the data extraction and some basic pharmacological data are illustrated in **Tables 3**, **4** and **5** respectively. In some articles, both *in vitro* and *in vivo* studies had been simultaneously performed. These studies are separately exhibited in both tables. The values of IC_{50} and its unit had been mentioned only based on their articles. However, the amounts of venoms in the articles with negative results had not been mentioned in IC_{50} column.

TABLE 3: SUMMARY OF INCLUDED ARTICLES ON PERFORMANCE OF SCORPION VENOM AND ITS COMPONENTS IN CANCER CELL LINES GROWTH INHIBITION (*IN VITRO* STUDIES)

Cell line	Organism	Disease	Scorpion species	Crude venom / component	IC_{50}	Result
Hep G2	human	hepatocellular carcinoma	*Mesobuthus martensii* Karsch, 1879	Anti-cancer peptide fraction III	200 mg/l	Positive [7]
K562	human	chronic myelogenous leukemia	*Heterometrus benga-lensis* C.L. Koch, 1841	Crude venom	88.3 µg/ml	Positive [8]
U937	human	histiocytic lymphoma	*Heterometrus benga-*	Crude venom	41.5 µg/ml	Positive [8]

			lensis C.L. Koch, 1841			
SHG-44	human	glioma	*Mesobuthus martensii* Karsch, 1879	recombinant chlorotoxin-like peptide	0.28 µM	Positive [9]
U937	human	histiocytic lymphoma	*Heterometrus bengalensis* C.L. Koch, 1841	Bengalin	3.7 µg/ml	Positive [10]
K562	human	chronic myelogenous leukemia	*Heterometrus bengalensis* C.L. Koch, 1841	Bengalin	4.1 µg/ml	Positive [10]
C6	rat	glioma	*Mesobuthus martensii* Karsch, 1879	131I-BmK CT	2 µg/ml	Positive [11]
SKBR3	human	breast adenocarcinoma	*Tityus discrepans* Karsch, 1879	neopladine 1	1 µg/µl	Positive [12]
SKBR3	human	breast adenocarcinoma	*Tityus discrepans* Karsch, 1879	neopladine 2	1 µg/µl	Positive [12]
C6	rat	glioma	*Mesobuthus martensii* Karsch, 1879	131I-BmK CT	2 µg/ml	Positive [11]
U87	human	glioblastoma	*Androctonus australis* Linnaeus, 1758	sAaCtx	125 µM	Positive [13]
C6	rat	glioma	*Mesobuthus martensii* Karsch, 1879	rAGAP	2 µM	Positive [14]
SH-SY5Y	human	neuroblastoma	*Androctonus crassicauda* Olivier 1809	crude venom	207.7µg/ml	Positive [15]
MCF-7	human	breast adenocarcinoma	*Androctonus crassicauda* Olivier 1809	crude venom	269 µg/ml	Positive [15]
C6	rat	glioma	*Mesobuthus martensii* Karsch, 1879	Lithium chloride and chlorotoxin	0.56 µM	Positive [16]
HeLa	human	cervical adenocarcinoma	*Leiurus quinquestriatus hebraeus* Hemprich & Ehrenberg, 1829	Platinum(IV)-chlorotoxin (CTX) conjugates	10.7 µM	Positive [17]
A549	human	lung carsinoma	*Leiurus quinquestriatus hebraeus* Hemprich & Ehrenberg, 1829	Platinum(IV)-chlorotoxin (CTX) conjugates	12 µM	Positive [17]
MCF-7	human	breast adenocarcinoma	*Leiurus quinquestriatus hebraeus* Hemprich & Ehrenberg, 1829	Platinum(IV)-chlorotoxin (CTX) conjugates	14 µM	Positive [17]
HeLa	human	cervical adenocarcinoma	*Hemiscorpius lepturus* Peters, 1861	ICD-85	26.62 µg/ml	Positive [18]
Jurkat	human	acute T- cell leukemia	*Mesobuthus martensii* Karsch, 1879	SVCIII	39.6 µg/ml	Positive [19]
THP-1	human	acute monocytic leukemia	*Mesobuthus martensii* Karsch, 1879	SVCIII	29 µg/ml	Positive [19]
HeLa	human	cervical adenocarcinoma	*Mesobuthus martensii* Karsch, 1879	crude venom	34.5 µg/ml	Positive [20]
DU145	human	prostat carcinoma	*Androctonus mauritanicus* Pocock, 1902	Mauriporin	4.4 µM	Positive [21]
LNCAP	human	prostat carcinoma	*Androctonus mauritanicus* Pocock, 1902	Mauriporin	7.8 µM	Positive [21]
PC-3	human	grade iv, prostat adenocarcinoma	*Androctonus mauritanicus* Pocock, 1902	Mauriporin	7.7 µM	Positive [21]
HeLa	human	cervical adenocarcinoma	*Centruroides limpidus limpidus* Wood, 1863	crude venom	-	Negative [22]
K562	human	chronic myelogenous leukemia	*Rhopalurus junceus* Herbst, 1800	crude venom	-	Negative [23]
U937	human	histiocytic lymphoma	*Rhopalurus junceus* Herbst, 1800	crude venom	-	Negative [23]
A549	human	lung carsinoma	*Rhopalurus junceus* Herbst, 1800	crude venom	0.63 mg/ml	Positive [23]
MDA-MB 468	human	mammary gland adenocarcinoma	*Rhopalurus junceus* Herbst, 1800	crude venom	0.64 mg/ml	Positive [23]
NCI-H292	human	mucoepidermoid pulmonary carcinoma	*Rhopalurus junceus* Herbst, 1800	crude venom	0.68 mg/ml	Positive [23]
MDA-MB 231	human	mammary gland adenocarcinoma	*Rhopalurus junceus* Herbst, 1800	crude venom	0.7 mg/ml	Positive [23]
Hep-2	human	larynx carcinoma	*Rhopalurus junceus* Herbst, 1800	crude venom	0.79 mg/ml	Positive [23]
HT-29	human	colorectal adenocarcinoma	*Rhopalurus junceus* Herbst, 1800	crude venom	0.89 mg/ml	Positive [23]

Siha	human	squamous cell carcinoma	*Rhopalurus junceus* Herbst, 1800	crude venom	0.91 mg/ml	Positive [23]
HeLa	human	cervical adenocarcinoma	*Rhopalurus junceus* Herbst, 1800	crude venom	1.05 mg/ml	Positive [23]
Raji	human	burkitt's lymphoma	*Rhopalurus junceus* Herbst, 1800	crude venom	-	Negative [23]
SW480	human	colon carsinoma	*Mesobuthus martensii* Karsch, 1879	rAGAP	18.4 µM	Positive [24]
MCF-7	human	breast adenocarcinoma	*Tityus serrulatus* Lutz & Mello, 1922	TsAP-S1	2.1 µM	Positive [25]
U251-MG	human	glioma	*Tityus serrulatus* Lutz & Mello, 1922	TsAP-S1	1.8 µM	Positive [25]
PC-3	human	grade iv, prostat adenocarcinoma	*Tityus serrulatus* Lutz & Mello, 1922	TsAP-S1	2.9 µM	Positive [25]
H838	human	non-small cell lung cancer	*Tityus serrulatus* Lutz & Mello, 1922	TsAP-2	11µM	Positive [25]
PC-3	human	grade iv, prostat adenocarcinoma	*Tityus serrulatus* Lutz & Mello, 1922	TsAP-2	13.3µM	Positive [25]
U251-MG	human	glioma	*Tityus serrulatus* Lutz & Mello, 1922	TsAP-2	15.4µM	Positive [25]
H157	human	lung adenocarcinoma	*Tityus serrulatus* Lutz & Mello, 1922	TsAP-2	4.1 µM	Positive [25]
H838	human	non-small cell lung cancer	*Tityus serrulatus* Lutz & Mello, 1922	TsAP-1	52.5 µM	Positive [25]
H157	human	lung adenocarcinoma	*Tityus serrulatus* Lutz & Mello, 1922	TsAP-1	55.9 µM	Positive [25]
MCF-7	human	breast adenocarcinoma	*Tityus serrulatus* Lutz & Mello, 1922	TsAP-2	6.4 µM	Positive [25]
K562	human	chronic myelogenous leukemia	*Mesobuthus martensii* Karsch, 1879	BmKKx2	6.7 nM	Positive [26]
HeLa	human	cervical adenocarcinoma	*Hemiscorpius lepturus* Peters, 1861	ICD-85 NPs	15.5 µg/ml	Positive [27]
irradiated M-NFS-60	mouse	myelogenous leukemia	*Mesobuthus martensii* Karsch, 1879	SVPII	-	Negative [28]
HSC4	human	oral squamous carcinoma	*Mesobuthus martensii* Karsch, 1879	BmKn2	17.26 µM	Positive [29]
SW620	human	colorectal adenocarcinoma	*Mesobuthus martensii* Karsch, 1879	BmKn2	40 µM	Positive [29]
MDA-MB-435S	human	previously described as ductal carcinoma	*Androctonus crassi-cauda* Olivier 1809	AcrAP1	2.9×10^{-6} M	Positive [30]
NCI-H460	human	large cell lung cancer	*Androctonus crassi-cauda* Olivier 1809	AcrAP1	2.7×10^{-6} M	Positive [30]
MDA-MB-435S	human	previously described as ductal carcinoma	*Androctonus crassi-cauda* Olivier 1809	AcrAP2	2.7×10^{-6} M	Positive [30]
MCF-7	human	breast adenocarcinoma	*Androctonus crassi-cauda* Olivier 1809	AcrAP1	3.3×10^{-6} M	Positive [30]
PC-3	human	grade iv, prostat adenocarcinoma	*Androctonus crassi-cauda* Olivier 1809	AcrAP1	2.06×10^{-6} M	Positive [30]
MCF-7	human	breast adenocarcinoma	*Androctonus crassi-cauda* Olivier 1809	AcrAP2	3.5×10^{-6} M	Positive [30]
NCI-H460	human	large cell lung cancer	*Androctonus crassi-cauda* Olivier 1809	AcrAP2	3.6×10^{-6} M	Positive [30]
PC-3	human	grade iv, prostat adenocarcinoma	*Androctonus crassi-cauda* Olivier 1809	AcrAP2	2.9×10^{-6} M	Positive [30]
C6	rat	glioma	*Mesobuthus martensii* Karsch, 1879	LiCl and pEGFP-N1-BmK CT	50 mM	Positive [31]
SMMC 7721	human	hepatocellular carcinoma	*Mesobuthus martensii* Karsch, 1879	LMWSVP	5.6 µg/ml	Positive [32]
HeLa	human	cervical adenocarcinoma	*Mesobuthus martensii* Karsch, 1879	LMWSVP	-	Negative [32]
MCF-7	human	breast adenocarcinoma	*Mesobuthus martensii* Karsch, 1879	crude venom	600 µg/ml	Positive [33]
SMMC7721	human	hepatocellular carcinoma	*Mesobuthus martensii* Karsch, 1879	crude venom	600 µg/ml	Positive [33]
U87	human	glioblastoma	*Scorpiops jendeki* Kovařík, 1994	rSj7170	-	Negative [34]
C6	rat	glioma	*Leiurus quinquestria-*	CTX-GO/DOX	5 µg/ml	Positive

			tus Hemprich & Ehrenberg, 1829			[35]
KYSE-510	human	esophageal squamous carcinoma	*Heterometrus liangi* Zhu & Yang, 2007	crude venom	50-100 µg/ml	Positive [36]
HSC-4	human	oral squamous carcinoma	*Mesobuthus martensii* Karsch, 1879	BmKn-2 peptide	29 µg/ml	Positive [37]
SHG-44	human	glioma	*Leiurus quinquestria-tus* Hemprich & Ehrenberg, 1829	CTX-Onc conjugate	20 µg/ml	Positive [38]
U251-MG	human	glioma	*Leiurus quinquestria-tus* Hemprich & Ehrenberg, 1829	CTX-Onc conjugate	20 µg/ml	Positive [38]
MDA-MB-231	human	breast adenocarcinoma	*Androctonus bicolor* Ehrenberg, 1828	crude venom	100 µg/ml	Positive [39]
HCT-116	human	colorectal carcinoma	*Androctonus crassi-cauda* Olivier 1809	crude venom	100 µg/ml	Positive [39]
HCT-8	human	ileocecal colorectal adenocarcinoma	*Androctonus crassi-cauda* Olivier 1809	crude venom	100 µg/ml	Positive [39]
MDA-MB-231	human	breast adenocarcinoma	*Leiurus quinquestria-tus* Hemprich & Ehrenberg, 1829	crude venom	100 µg/ml	Positive [39]
MCF-7	human	breast adenocarcinoma	*Androctonus amoreuxi Audouin, 1826*	crude venom	0.61 µg/ml	Positive [40]
U251	human	glioma	*Mesobuthus martensii* Karsch, 1879	CA4	6 µM	Positive [41]
F98	rat	glioma	*Mesobuthus martensii* Karsch, 1879	CA4	6 µM	Positive [41]
U251	human	glioma	*Mesobuthus martensii* Karsch, 1879	CTX-23	6 µM	Positive [41]
F98	rat	glioma	*Mesobuthus martensii* Karsch, 1879	CTX-23	6 µM	Positive [41]
MCF-7	human	breast adenocarcinoma	*Vaejovis smithi Pocock*, 1902	VmCT1	25 µmol/L	Positive [42]
PC-3	human	grade iv, prostat adenocarcinoma	*Androctonus amore-uxi* Audouin, 1826	crude venom	3.04 µ g/mL	Positive [43]
HCT-8	human	Ileocecal colorectal adenocarcinoma	*Androctonus bicolor* Ehrenberg, 1828	liposomes and encapsulation of venom	200 µg/mL	Positive [44]
MDA-MB-231	human	breast adenocarcinoma	*Rhopalurus junceus* Herbst, 1800	crude venom	0.75 mg/ml	Positive [45]
HCT-8	human	ileocecal colorectal adenocarcinoma	*Androctonus crassi-cauda* Olivier 1809	crude venom	80 µg/mL	Positive [46]
MDA-MB-231	human	breast adenocarcinoma	*Androctonus crassi-cauda* Olivier 1809	crude venom	80 µg/mL	Positive [46]

TABLE 4: SUMMARY OF INCLUDED ARTICLES ON PERFORMANCE OF SCORPION VENOM AND ITS COMPONENTS IN CANCER CELL LINES GROWTH INHIBITION (*IN-VIVO* STUDIES)

Cell line	Organism	Disease	Crude venom/component	Result
C6	rat	glioma	BmKCT	Reduction in tumor size [47]
H22	mouse	hepatoma	PESV during 5-Fu chemotherapy	Reduction in tumor volume [48]
LLC	mouse	lewis lung carcinoma	PESV during Cyclophosphamide chemotherapy	Reduction in tumor volume [49]
H22	mouse	hepatoma	PESV during chemotherapy	Reduction in some angiogenesis factor [50]
LLC	mouse	lewis lung carcinoma	CTX + PESV	Reduction in tumor volume [51]
C6	rat	glioma	Ad-BmK CT	Reduction in tumor volume [52]
H22	mouse	hepatoma	PESV combined 5-fluorouracil (5-Fu)	Reduction in tumor volume [53]
Sarcoma 180	mouse	sarcoma	BmK AGAP-SYPU2	Increased survival of mice [54]
H22	mouse	hepatoma	PSV combined with 5-fluorouracil (5-Fu)	Reduction in tumor volume [55]
SKOV3	human	ovarian adenocarcinoma	PESV	Reduction in tumor growth [56]
SHG-44	human	glioma	Chlorotoxin CTX-conjugated Onc	Reduction in tumor volume [57]
U251	human	glioma	CTX-Onc conjugate	Reduction in tumor volume [38]
MCF-7	human	breast adenocarcinoma	Crude venom	Reduction in tumor volume [40]

TABLE 5: SOME BASIC PHARMACOLOGICAL DATA ABOUT THE SCORPION VENOM AND ITS COMPONENT HAVE BEEN USED IN *IN VITRO* AND *IN VIVO* STUDIES

Scorpion species	Crude venom/component	Venom/ isolated venom component/ re-combinant	Dose range	Minimal active concentration	Model
Mesobuthus martensii Karsch, 1879	anti-cancer peptide fraction III	isolated venom component	0 - 200 mg/l	5 mg/l	*in vitro* [7]
Heterometrus bengalensis C.L. Koch, 1841	crude venom	venom	0 – 200 µg/ml	10 µg/ml	*in vitro* [8]
Mesobuthus martensii Karsch, 1879	recombinant chlorotoxin-like peptide	re-combinant	0 - 0.14 µM	0.07 µM	*in vitro* [9]
Tityus discrepans Karsch, 1879	neopladine 1	isolated venom component	0-30 µg/ml	1 µg/ml	*in vitro* [12]
Tityus discrepans Karsch, 1879	neopladine 2	isolated venom component	0-30 µg/ml	1 µg/ml	*in vitro* [12]
Heterometrus bengalensis C.L. Koch, 1841	Bengalin	isolated venom component	0 - 20 µg/ml	1 µg/ml	*in vitro* [10]
Androctonus australis Linnaeus, 1758	sAaCtx	isolated venom component	0-200 µM	5 µM	*in vitro* [13]
Androctonus crassicauda Olivier 1809	crude venom	venom	0 -200 µg/ml	10 µg/ml	*in vitro* [15]
Mesobuthus martensii Karsch, 1879	rAGAP	re-combinant	0-40 µM	5 µM	*in vitro* [14]
Mesobuthus martensii Karsch, 1879	Lithium chloride and chlorotoxin	isolated venom component	0- 2.24 µM	0.56 µM	*in vitro* [16]
Leiurus quinquestriatus hebraeus Hemprich & Ehrenberg, 1829	Platinum(IV)-chloro-toxin (CTX) conjugates	isolated venom component	0–16 µM	1 µM	*in vitro* [17]
Hemiscorpius lepturus Peters, 1861	ICD-85	isolated venom component	8×10^{-4} - 60 µg/ml	2 µg/ml	*in vitro* [18]
Mesobuthus martensii Karsch, 1879	SVCIII	isolated venom component	0 - 50 µg/ml	1 µg/ml	*in vitro* [19]
Androctonus mauritanicus Pocock, 1902	Mauriporin	isolated venom component	0- 60 µM	5 µM	*in vitro* [21]
Centruroides limpidus limpidus Wood, 1863	crude venom	venom	0-400 µg/100 µl	50 µg/100 µl	*in vitro* [22]
Rhopalurus junceus Herbst, 1800	crude venom	venom	0 - 1 mg/ml	0.1 mg/ml	*in vitro* [23]
Mesobuthus martensii Karsch, 1879	rAGAP	re-combinant	0 - 80 µM	5 µM	*in vitro* [24]
Tityus serrulatus Lutz & Mello, 1922	TsAP-S1	isolated venom component	0- 160 µM	5 µM	*in vitro* [25]
Tityus serrulatus Lutz & Mello, 1922	TsAP-2	isolated venom component	0- 160 µM	5 µM	*in vitro* [25]
Hemiscorpius lepturus Peters, 1861	ICD-85 NPs	isolated venom component	8×10^{-4} - 56 µg/ml	8×10^{-4} µg/ml	*in vitro* [27]
Mesobuthus martensii Karsch, 1879	SVPII	isolated venom component	0-3 mg/l	1 mg/l	*in vitro* [28]
Mesobuthus martensii Karsch, 1879	BmKn2	isolated venom component	0-24.28 µM	2.97 µM	*in vitro* [29]
Mesobuthus martensii Karsch, 1879	LiCl and pEGFP-N1-BmK CT	isolated venom component	0-50 mM	10 mM	*in vitro* [31]
Mesobuthus martensii Karsch, 1879	LMWSVP	isolated venom component	0- 800 µg/ml	100 µg/ml	*in vitro* [32]
Mesobuthus martensii Karsch, 1879	crude venom	venom	0-800 µg/ml	100 µg/ml	*in vitro* [33]
Mesobuthus martensii (Karsch, 1879)	BmK AGAP-SYPU2	isolated venom component	0.5- 4 mg/kg	-	*in vivo* [34]
Scorpiops jendeki Kovařík, 1994	rSj7170	re-combinant	0 - 10 µM	2 µM	*in vitro* [34]
Leiurus quinquestriatus Hemprich & Ehrenberg, 1829	CTX-GO/DOX	isolated venom component	0- 5 µg/ml	1 µg/ml	*in vitro* [35]
Heterometrus liangi Zhu & Yang, 2007	crude venom	venom	0-100 µg/ml	50 µg/ml	*in vitro* [36]
Leiurus quinquestriatus Hemprich & Ehrenberg, 1829	CTX-Onc conjugate	isolated venom component	0-100 µg/ml	2 µg/ml	*in vitro* [38]
Leiurus quinquestriatus Hemprich & Ehrenberg, 1829	crude venom	venom	0-100 µg/ml	20 µg/ml	*in vitro* [39]
Androctonus amoreuxi Audouin, 1826	crude venom	venom	0 -100 µg/ml	0.01 µg/ml	*in vitro* [40]
Androctonus amoreuxi Audouin, 1826	Crude venom	venom	100 µg/ml	-	*in vivo* [40]
Mesobuthus martensii Karsch, 1879	CA4	isolated venom component	0-6 µM	0.5 µM	*in vitro* [41]
Mesobuthus martensii Karsch, 1879	CTX-23	isolated venom component	0-6 µM	0.5 µM	*in vitro* [41]

DISCUSSION: Severe deaths occur worldwide due to cancer as a most life-threatening disease. There is still a high rate of mortality related to cancer despite many therapeutic advances. Nowadays, four standard methods are adopted for cancer treatment: surgery, radiation therapy, chemotherapy, and immunotherapy [58]. To reduce and inhibit cell growth, specific chemical compounds are used through a chemoprevention study. More than 1,000 agents and agent combinations have been selected and accessed *via* preclinical chemopreventive testing programs since 1987. These activities have included *in vitro* mechanistic and cell-based transformation assays, as well as carcinogen-induced and transgenic animal models. New agents selected based on their preliminary efficacy, mechanisms, and potentialities for improving chemopreventive indices have been continuously regarded to be used in chemopreventive drugs [59]. Still, more potent anticancer drugs with fewer side effects are being continuously searched by oncologists since some can have adverse effects on other organs, such as nervous system, heart, liver, bladder, lungs, and kidney.

Cancer cell migration and proliferation may be affected by the specific binding of some isolated peptides or proteins to the cancer cell membrane [6]. Historically, scorpion venoms have been biochemically studied for a long time. Nevertheless, the great improvements in the technology of peptide / protein isolation and characterization over the past two decades have specifically coincided with the mentioned studies [25]. It is nearly a decade that the inhibitive properties of scorpion venom and its components have been specially focused on.

In this research, we collected the results of the anti-proliferation effects of scorpion venom and its components in the form of a systematic review for the first time. As the collected studies were divided into the two parts of *in-vitro* and *in-vivo* studies, the discussion was divided into two parts: 1) *in-vitro* studies; 2) *in-vivo* studies.

***In-vitro* Studies:** The findings of this study demonstrated that the studies on the anti-cancer effects of scorpion venom have been started since 2006. Before this, many articles were found with the key words of "cancer", "cell line", and "scorpion", but the researches had been focused on the venom cytotoxicity effects on cells to study its toxicity mechanism.

The first available comprehensive study had been done by Das Gupta *et al*., in 2007. They had made an effort to assess the anti-proliferative and apoptotic efficacy of crude venom extracted from *Heterometrus bengalensis* C. L. Koch, 1841, against the two human leukemic cell lines of U937 and K562. They had used some experimental methods, such as comet assay, flow cytometry, and scanning electron microscopy.

The mentioned venom had induced cell growth inhibition in U937 and K562 cell lines and their IC_{50} values had been reported to be 41.5 µg/ml and 88.3 µg/ml, respectively [8]. In 35 studies, cell lines were found to have been treated with crude venom and 29 various types of components had been applied for inducing apoptosis in them. The variable amount of crude venom ranges between 0.63 mg/ml [23] and 600 mg/ml [33].

In some studies, an astonishing subject was observed to strengthen the use of scorpion venom for cancer treatment hypothesis. The scorpion venom and its components had been shown to be able to inhibit the growth of cancer cell lines, while having no effects on the normal cells when using the same doses. For example in 2007, Fu and Yin *et al*., had produced a recombinant chlorotoxin-like peptide from scorpion *Buthus martensii* Karsch Karsch, 1879, to treat human glioma (SHG-44) cells with this recombinant peptide. They had shown that rBmK CTa inhibits the growth of glioma cells in a dose-dependent manner with an IC_{50} value equal to 0.28 µM.

Under the same conditions, the IC_{50} value for normal astrocytes had increased to 8 µM [9]. In 2013, Almaaytah and Tarazi *et al*., had found a synthetic replicate (Mauriporin) to exert potent selective cytotoxic and anti-proliferative activities against prostate cancer cell lines (IC_{50} 4.4 - 7.8 µM) as compared to non-tumorigenic cells (IC_{50} = 59.7 - 62.5 µM) [21]. Also, in 2013, Diaz-Garcia *et al*., had shown a significant reduction of cancer cell viability to be between a panel of cancer cell lines and normal cells treated with *Rhopalurus junceus*

(Herbst, 1800, venom. This venom had not affected the viability neither in the normal nor in the hematopoietic cell lines at the same concentrations [23].

Besides the inhibitive effects of scorpion venom on many cancer cell lines, there are some cells that are resistant to scorpion venom [22, 23, 25, 28, 32, 34]. The share of such cell lines in this study was 12% out of the total share mainly belonging to HeLa cell [22, 32].

An overview on articles showed that the most of studies have focused on only inhibitory effects of this venom and it's components on cancer cells lines. It seems that the studies will be more valuable, if the inhibitory effects be assessed simultaneously in cancer cell line and normal cells. Still, there were some scorpions, on which no *in vivo* studies had been done, for example *Hemiscorpius lepturus* Peters, 1861, as one of the most dangerous scorpion species.

On the other hand, as it can be seen in the most of articles, their concentration has been on the related apoptotic genes. It seems that the using of some methods such as Western blot in order to detecting of apoptotic genes products is essential.

***In-vivo* Studies:** All the 16 *in-vivo* treatments were found to be successful leading to reduced tumor size, weight, and volume. In some other researches, some angiogenesis factors were seen to have been reduced [50].

In 2010, the first available *in vivo* study had been accomplished by Fan *et al*., who had reported that proliferation and metastasis of glioma cells had been effectively inhibited by BmKCT due to having a selective affinity to glioma cells. It had been also suggested to be exploited as a potential therapeutic agent for glioma diagnosis [47]. In that same year, the mechanism and inhibitive effect of a scorpion venom polypeptide (PESV) on H22 tumor cell repopulation during 5-fluorouracil chemo-therapy had been studied by Wang *et al*., Thus, the inhibition of H22 tumor cell repopulation by PESV, probably through an anti-angiogenesis mechanism, was proved by them during 5-fluorouracil chemotherapy [48]. In 2011, cyclophosphamide as a tumor growth inhibitor had been used by Sun *et al*., to establish a cancer model. The polypeptide extracted from scorpion venom (PESV) had been applied to Lewis Lung Carcinomas (LLCs).

In 2013, a replication - defective adenovirus recombinant had been selected by Du *et al*., to deliver BmK CT gene to the C6 glioma cells. MMP-2 upregulation, which is partially responsible for the enhanced ability of glioma cell migration, can be specifically inhibited by BmKCT enzymatic activity when binding to it. Targeting BmK CT to C6 glioma cells specifically through this delivery system had been developed by them. Thus, the replication-defective recombinant adenovirus Ad-BmK CT could provide a powerful delivery system to treat glioblastoma [52]. In 2014, Shao *et al*., had undertaken isolating peptides with analgesic and antitumor activities from scorpion venom. BmK AGAP-SYPU2 as a new analgesic-antitumor peptide had been purified and characterized with bioassay-guided chromatography protocols. It had exhibited analgesic effects and antitumor activities during all the animal tests. The homology model of BmK AGAP-SYPU2 had represented the conservative structures of most scorpion venoms. The variant sites had been considered to be important for the specific pharmaceutical activities of this peptide. This kind of dual-function peptide with pain-relieving and antitumor effects was clinically valuable for improving patient survival without compromising his/her quality of life [54].

By conjugating scorpion venom and its components with other agents in some studies, their antitumor effects could be intensified. For example, in 1988, the northern leopard frog Rana Lithobates pipiens Schreber, 1782, oocytes had been first used to isolate Onconase (Onc) as a small RNase [60]. In 2015, Wang et al. and Guo had prepared Onc conjugated with CTX as a potential anti-glioma drug, in which the recombinant CTX covalently bonded with recombinant Onc *via* a reversible disulfide linkage. Thus, much higher cytotoxicity to the cultured U251 and SHG-44 glioma cells was obtained by chemically conjugating CTX and Onc compared to their physical mixture (CTX+Onc). Moreover, improved antitumor effects on the subcutaneous U251 or SHG-44 tumors of the nude mouse models had been achieved by the CTX-Onc conjugate compared to the CTX+Onc control. These results were indicative of the promotion of the tumor targeting of Onc through the chemically reversible conjugated CTX. Also, the present CTX-Onc conjugate as a potential drug targeting anti-glioma could be further developed [38].

The *in-vivo* investigations had not been limited to the evaluation of the antitumor effects of venom components. In a recent study published in 2016, Salem et al. had shown the cytotoxic effects of crude venom extracted from *Androctonus amoreuxi* Audouin, 1826, as an Egyptian scorpion on the MCF-7 human breast cancer cell line and Ehrlich Ascites Carcinoma (EAC) cells. Interestingly, venom had been shown to restore the altered biochemical and hematological parameters of animals bearing tumors and significantly prolong their lifespan. Consequently, the potential cytotoxic effects of *Androctonus amoreuxi* Audouin, 1826, on tumor cells through apoptotic, anti-proliferative, and anti-angiogenic activities had been evidenced by them so as to open a new path towards future studies on the anti-cancer effects of the mentioned agent [40].

On the whole, scorpion venom and its components were found to have a high rate of success in inducing apoptosis in various types of cancer cell lines. Also scorpion venom and derived molecules have shown their potential as tools for the fight on cancer in directly-acting therapeutic, diagnostic tags, adjuvants or just carriers for other relevant moieties [61]. Interestingly, no effects on the normal cells had been seen when the cancer cell lines and normal cells had been treated at the same time with the same doses. The mentioned agents had represented a novel potentially clinical therapeutic approach for cancer treatment.

CONCLUSION: This was the first systematic review includes some tables that provide valuable information to the reader on the therapeutic anti-cancer properties of scorpion venom and its components. The results demonstrated that this natural venom can induce apoptosis in various types of cancer cell lines.

Some studies were found to show that these agents are able to inhibit the growth of cancer cells, while having no effects on the normal cells with the same doses. Considering the adverse effects of anti-cancer drugs on other vital organs, we need to focus on the development of new drugs with potent anti-cancer and lower side effects. The findings of this research strongly reinforced this hypothesis that these agents provide a new efficient approach to cancer treatment.

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