Pharmacogn J. 2019; 11(4):712-717.
A Multifaceted Journal in the field of Natural Products and Pharmacognosy
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Original Article

Evaluation of Antispasmodic Effect of Arcapillin on Smooth Muscles of Rats

Lubna F. Abu-Niaaj[1,*], Ibrahim Katampe[1], Shtaywy S. Abdalla[2]

ABSTRACT

Background: Arcapillin, 2',4',5-trihydroxy-5',6,7–trimethoxyflavone, is a flavone aglycone isolated from several *Artemisia* species, though, it was first identified from *A. capillaris*. The *Artemisia* species are used in folk medicine as a remedy for gastrointestinal and liver illnesses, hypertension, fever and inflammation. Studies indicated a potential role of arcapillin to relieve symptoms of liver disorders; however, there is no report yet in the literature of its effect on smooth muscles. **Objective:** Our study aims to evaluate the effect of arcapillin, isolated from *A. monosperma,* on the contractile activity of rat smooth muscles. **Materials and Methods:** Increased concentrations of arcapillin were tested on isolated rat ileum, pulmonary artery, trachea, and urinary bladder. The muscle contraction was recorded upon addition of arcapillin in eight cumulative concentrations of half log units in the range of [10^{-7} M -3×10^{-4} M]. Depending on the organ-containing muscles, the preparations were treated with arcapillin either at basal tonus or after pre-stimulated via a contractile agent; 10^{-3} M O-acetylcholine on ileum and 10^{-5} M L-phenylephrine on pulmonary artery rings. Control tissues were treated with sodium hydroxide in an equivalent concentration to that used to dissolve the flavone. **Results:** Arcapillin caused a dose-dependent relaxation on ileum preparation and pulmonary artery. The inhibition of the contractile activity of ileum was reversible within 60 seconds after washing off the flavone. The urinary bladder showed a slight increase in contraction at the highest concentrations starting at [10^{-4} M] of arcapillin. There was no observed effect on the contraction of tracheal smooth muscles by all tested concentrations of arcapillin. **Conclusion**: The antispasmodic activity of arcapillin may contribute to the pharmaceutical importance of *A. monosperma* in particularly to treat gastrointestinal disorders.

Key words: Arcapillin, *Artemisia monosperma*, Flavone, Antispasmodic, Smooth Muscles.

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History

- Submission Date: 24-11-2018;
- Review completed: 06-04-2019;
- Accepted Date: 19-04-2019.

DOI : 10.5530/pj.2019.11.113

Article Available online

http://www.phcogj.com/v11/i4

INTRODUCTION

Artemisia monosperma (Delile) is among the *Artemisia* species used in traditional medicine mainly for the treatment of gastrointestinal and liver disorders,[1] diabetes,[2] inflammation, and fever.[3] It is also known to relieve menstruation pain and to induce labor.[4-7] An air-dried powdered drug of the plant exhibited antispasmodic activity in the treatment of colic or in conditions associated with arterial hypertension.[1] Different extracts of *A. monosperma* exhibited a wide spectrum of biological actions such as muscle relaxation,[6-8] antidiabetic,[1,8] and antimicrobial activities.[9-14] Bioactive compounds isolated from *Artemisia* species showed antispasmodic,[15,16] antihypertensive,[17] antimicrobial,[12,13] insect repellents,[18-20] antitumor and anti-inflammatory activities.[21-23] Arcapillin was first identified from *A. capillaris*[24] and it was reported an antihepatotoxic.[25-27] There is no study yet to highlight the effects of arcapillin on vertebrate muscles. This study aims to evaluate the effect of arcapillin on the contractile activity of rat smooth muscles.

MATERIALS AND METHODS

Isolation of Arcapillin

Arcapillin was isolated from the methanol extract of *Artemisia monosperma* (Delile). A description of the protocol used for the isolation of this flavone and the methodologies for its identification is detailed in Abu-Niaaj and Katampe 2018.[28]

Animals and preparations of smooth muscle tissues

Male and female virgin rats (150-250 g) were used to obtain ileum, trachea, pulmonary artery and urinary bladder. Animals were housed at standard conditions with adequate access to food and water. The research was conducted in accordance with the internationally accepted guidelines for Laboratory Animal Care and Use (NIH publication number 85-23; revised 1985). The selected organs were obtained immediately after euthanizing the animal and were placed in an oxygenated Physiological Salt Solution (PSS) at 37°C ± 0.5 to be cleaned gently from surrounding connective tissue. The ileum was flushed twice with PSS to remove contents then cut into 1-2 cm long pieces. The urinary bladder was cut from the neck region and from the distal end to allow insertion of a polyethylene tube into its lumen. The organ was flushed with aerated PSS and pieces of 3-5 mm were obtained from the middle region. The trachea and pulmonary artery were cut into 3-5 mm rings after inserting fine polyethylene tubing into the lumen to avoid injury during surgical manipulation. For each set of experiment, two tissue pieces were used;

Cite this article: Abu-Niaaj LF, Katampe I, Abdalla SS. Evaluation of Antispasmodic Effect of Arcapillin on Smooth Muscles of Rats. Pharmacog J. 2019;11(4):712-7.

one piece was treated with increasing cumulative concentrations of arcapillin while the other piece was control treated with NaOH solution as it was used to dissolve arcapillin. Each tissue piece was individually mounted in glass tissue bath filled with warm PSS at 37°C, continuously aerated with 95% O_2:5% CO_2. The piece of tissue was tied at one end by a thread to a glass hook fixed at the bottom of the tissue bath, while the other end of the tissue was tied by a long thread connected to the transducer connected to the oscillography. Appropriate tensions were applied on tissues; 2.5 g on ileum and urinary bladder, and a tension of 3.5 g was applied on the pulmonary artery and tracheal rings. The isometric contraction of muscle preparations was recorded using force transducers (UF1) connected to a Palmer Bioscience (England) oscillography.

Preparation of solutions

Arcapillin solution

Arcapillin stock solution was prepared by dissolving the entire quantity (180 mg) isolated from *A.monosperma*[28] in 0.1 N NaOH (3 ml) and the volume was completed to 10 ml using PSS. The solution was refrigerated in a dark bottle to avoid photooxidation and/or degradation. Working solutions were prepared shortly before use and warmed to 37°C in a water bath before added to tissues.

Physiological salt solution (PSS)

Fresh PSS buffer was prepared prior to the experiment by dissolving salt ingredients in distilled water to obtain (mM): NaCl 118; KCl 4.7; $CaCl_2$ 2.5; $MgCl_2$ 0.5; NaH_2PO_4 1.0; $NaHCO_3$ 25.0; glucose 11.1. The pH was adjusted to 7.4 and the buffer was continuously aerated with 95% O_2:5% CO_2. The temperature was maintained at 37°C in a water bath before use.

Other solutions

The stock and working solutions of L-phenylephrine hydrochloride (Tokyo, Kasei, TCI) were prepared using saline. Papaverine hydrochloride solutions were prepared using distilled water. All stock solutions were refrigerated immediately after preparation. Promptly before use, working solutions were prepared and warmed in a water bath to 37°C.

Protocol for experimentation on tissues

Tissues were allowed to equilibrate in tissue baths for 60 min in oxygenated PSS buffer at 37°C ± 0.5, except for the urinary bladder which was allowed to equilibrate for 45 min. The buffer was changed every 15 min to wash out metabolites. After equilibration, pulmonary artery rings were precontracted with 10^{-5} M L-phenylephrine and allowed to equilibrate for 25-30 min before establishment of the concentration-effect curve of arcapillin. Control tissues were treated with NaOH using the same concentration used to dissolve arcapillin. The concentration-effect curve for the treated tissue with arcapillin was established by adding eight cumulative concentrations of half log units increase in the range of [10^{-7} M-3×10^{-4} M]. After addition of the highest concentration, the ileum and pulmonary artery rings were subjected to 10^{-3} M papaverine to induce maximum relaxation which was expressed as 100% tissue relaxation. The relaxation induced by arcapillin was then calculated as a percentage in reference to the maximum relaxation caused by papaverine.

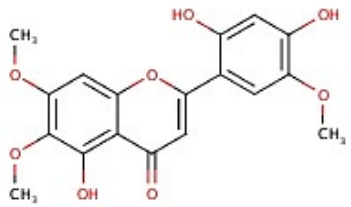
Statistical analysis

Data are presented as mean ± standard error of the mean (SEM). *t*-test was calculated for paired samples to compare the control samples to those treated with arcapillin and differences were considered significant when $P < 0.05$. The value of the half maximum effective concentration (EC_{50}) of arcapillin on ileum and pulmonary artery were visually fitted from experimental plots as shown in Figure 3.

RESULTS

Identification of Arcapillin

Arcapillin, a 2',4',5-trihydroxy-5',6,7–trimethoxyflavone, was identified for the first time from *A. monosperma.*[28] It was characterized using TLC, MS, NMR, and UV chemical fingerprinting methods. The ^{1}H-NMR and MS are shown in Figure 1.



Physiological effect of Arcapillin on rat smooth muscles

Arcapillin in the range of 10^{-7} M-3×10^{-4} M caused a concentration-dependent relaxation of the tone and phasic contraction of the ileal segments. This inhibition was reversible within one minute upon washing the tissue with PSS (Figures 2A and 3A). Arcapillin caused a tone relaxation of L-phenylephrine-precontracted pulmonary artery rings in a concentration-dependent manner (Figures 2B and 3B). Compared to the maximum relaxation caused by 10^{-3} M papaverine, the induced inhibition induced by highest concentration (10^{-4} M) of arcapillin was 65.6% ± 6.4 ($P < 0.05$) on ileum, and 70.9% ± 4.9 ($P < 0.02$) on pulmonary artery (Table 1). The calculated EC_{50} of arcapillin from the experimental plots in Figure 3 were (2.8 ± 0.6) 10^{-5} M on the ileum and (5.8 ± 0.6)10^{-5} M on the pulmonary artery. The urinary bladder showed a slight increase of the phasic contractions at higher concentrations (3×10^{-5} to 3×10^{-4} M); however, no effect was observed at the low concentrations (10^{-7} to 10^{-5} M) (Figure 2C). Arcapillin showed no effect on the contractile tone of the tracheal rings (data not shown).

DISCUSSION

Flavonoids are bioactive compounds with a wide spectrum of biological activities including their effects on smooth muscles.[8,15,16,29,30] *Artemisia monosperma* is a good source of flavonoids and is reputed in folk medicine in the Middle East for the relief of abdominal illness, inflammation and for inducing labor. Several flavonoids isolated from *A. monosperma* were reported to induce relaxation of different rat smooth muscles.[15-16] We reported the first-time isolation of arcapillin from *A.monosperm.*[28] This study aim was to evaluate the pharmacological effects of this flavone on vertebrate smooth muscle which has not yet reported in the literature. Our data show a disparity of effects on isolated rat smooth muscles of different organs upon being treated with arcapillin. There was a significant inhibition of the contractile activity of ileum and pulmonary artery but a slight increase in the contraction of urinary bladder at a concentration higher than 3×10^{-5} M. There was no effect observed on the tone of tracheal muscles. The difference in arcapillin effects on rat smooth muscles might be due to the diverse properties of these muscles in different organs or maybe caused by different mechanisms of action. Flavonoids were reported as blockers for ion channels including those for calcium and potassium.[30-33] They also act as inhibitors of selective enzymes including cyclic AMP phosphodiesterase.[34-36] Arcapillin was reported as an inhibitor of α-glucosidase, and as a protein tyrosine phosphatase 1B.[37,38] Tyrosine kinase inhibitors reduce the amplitudes of contractions of intact smooth muscle stimulated by muscarinic or

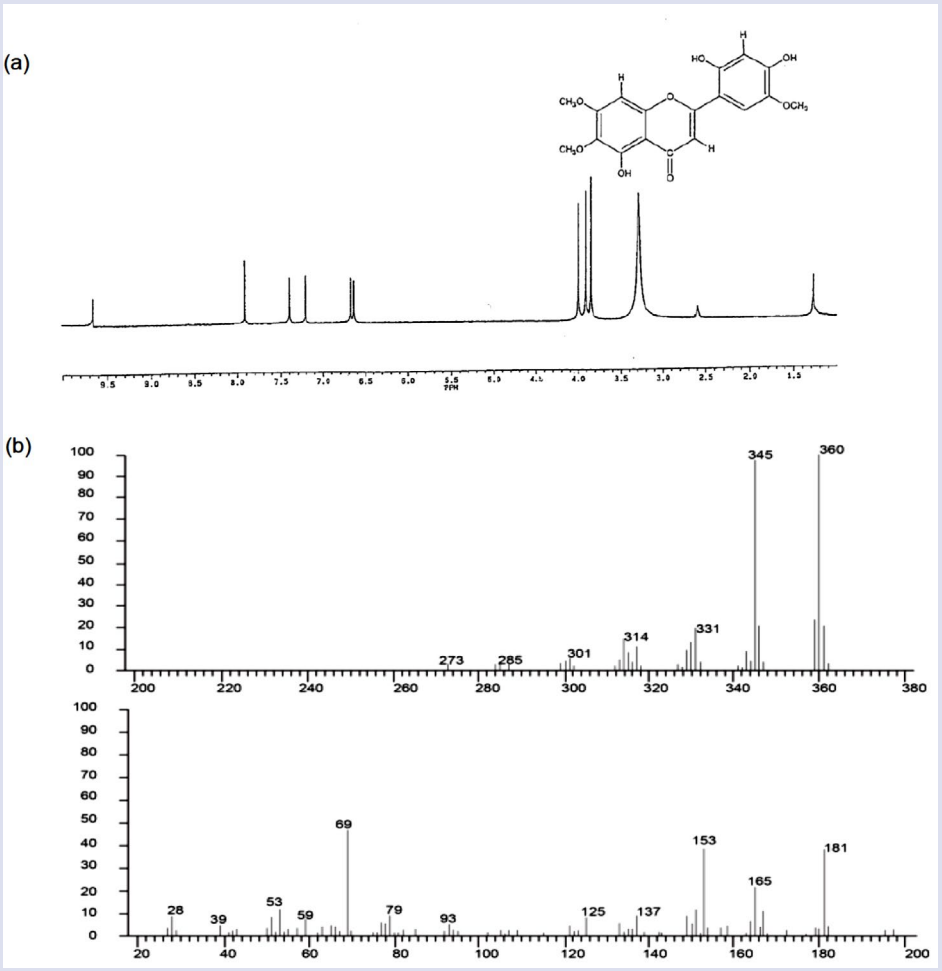


Figure 1: ^{1}H-Nuclear magnetic resonance (a) and Mass spectroscopy (b) of Arcapillin.

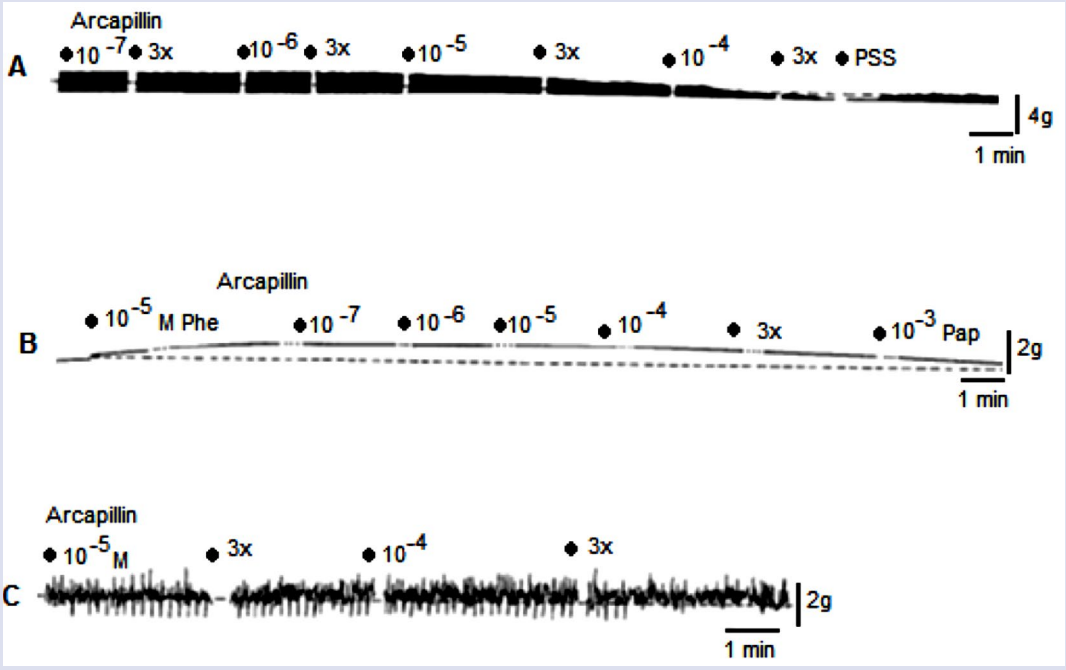


Figure 2: Typical traces showing effects of increasing concentrations of arcapillin on rat isolated tissues: (A) ileum, (B) Pulmonary artery, and (C) urinary bladder.

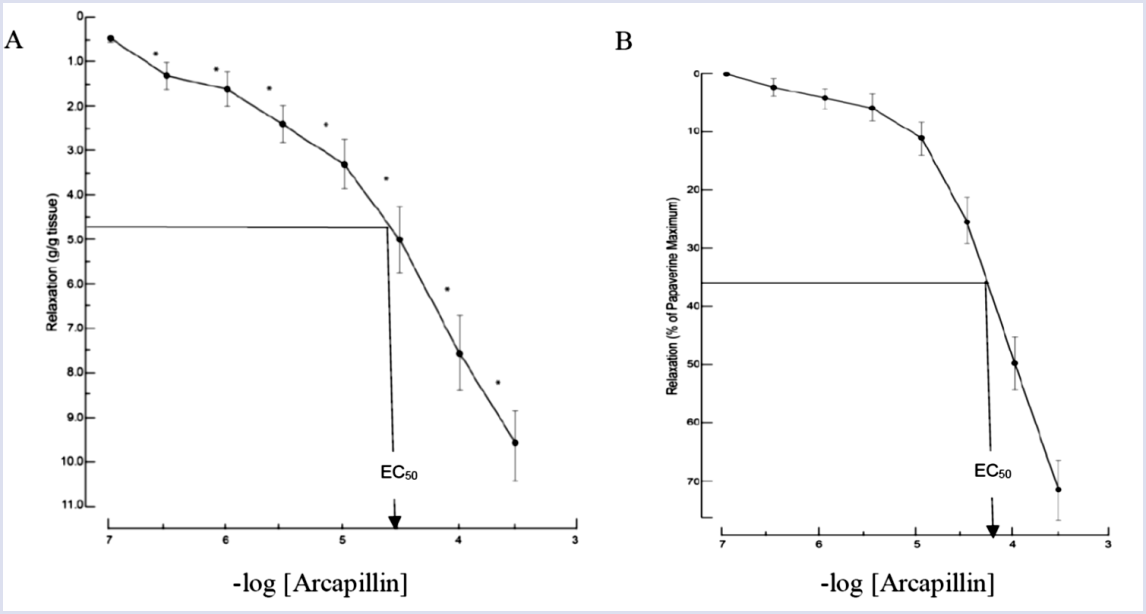


Figure 3: Arcapillin concentration-effect curves (A) ileal muscles (B) pulmonary artery. Vertical bars represent SEM. The EC_{50} of arcapillin on ileum and pulmonary artery were visually fitted from the experimental plots as shown on the graph.

Table 1: Arcapillin EC_{50} on rat ileum and pulmonary artery and the % maximum relaxation induced by arcapillin compared to that % of papaverine maximum[a].

Tissue	N[b]	EC_{50} (M)	% Max. relaxation induced by Arcapillin compared to the max. relaxation caused by 10^{-3} M Papaverine
Ileum	9	$(2.8 \pm 0.6)\ 10^{-5}$	65.6 ± 6.4 ($P < 0.05$)
Pulmonary artery	9	$(5.8 \pm 0.6)\ 10^{-5}$	70.9 ± 4.9 ($P < 0.02$)

[a]Data are presented as mean ±SEM; [b]N=Number of experiments

α-adrenergic agonists.[39] It is possible that the relaxant effect of arcapillin on ileum and pulmonary artery is caused by the decreased cytosolic calcium concentration which subsequently affects calcium availability to the intracellular proteins, or might be due to the activation of potassium channels.[30-34] It is also possible that the induced relaxation of ileum by arcapillin is due to the inhibition of the phosphodiesterase enzyme causing an elevation in the cellular cAMP; however, the increased contractility of the urinary bladder could be due to affecting the α-adrenergic receptors.[33,34,39] Overall, the antispasmodic activity of arcapillin is moderate compared to other flavones which most likely caused by its structural configuration as a 2',4',5-trihydroxy-5',6,7-trimethoxyflavone. It is known that the diversity of functional groups of flavonoids contributes to their variable biological activities and potency.[40] Structural-activity studies show that the number and position of methyl and hydroxyl groups of flavonoids influence the strength of their bioactivity. Studies showed that methylated flavonoids at the 7-position with a free hydroxyl group at the 2´position are less effective as bioactive compounds.[36] The absence of a hydroxyl group at position 3 in flavones showed a decreased antioxidant activity[38]. It was shown that the presence of more hydroxyl groups at the 3',4',5, and 7 positions increased effectiveness of flavones in inhibiting the formation of advanced glycation end products.[41,42] Flavones with more hydroxyl groups at 4',5',6',6 were reported to induce higher *ex vivo* relaxant effect on tracheal rat muscle.[43] Furthermore, studies showed that flavones having free hydroxyl groups in the ortho positions at carbons 5 and 7 of the A- ring were more potent bioactive than those lacking this configuration.[44] Collectively, the structure of arcapillin may explain its moderate bioactivity in this study. The precise mechanism of action on muscles should be further investigated.

CONCLUSION

This study demonstrates that arcapillin has a significant spasmolytic activity on the intestinal smooth muscles, which justifies the use of *A. monosperma* to relieve pain of gastrointestinal disorders. It is most likely that this flavone may be responsible in part of the pharmaceutical importance of *Artemisia* species which are rich in bioactive flavonoids.

ACKNOWLEDGEMENT

The authors acknowledge Central State University and the University of Jordan for the provided technical support.

CONFLICTS OF INTEREST

The authors declared no conflicts of interest.

ABBREVIATIONS

TLC: Thin Layer Chromatography; MS: Mass Spectroscopy; NMR: Nuclear Magnetic Resonance; UV: Ultraviolet; NaCl: Sodium Chloride; KCl: Potassium Chloride; $CaCl_2$: Calcium Chloride; $MgCl_2$: Magnesium Chloride; NaH_2PO_4: Sodium Dihydrogen Phosphate; $NaHCO_3$: Sodium Bicarbonate.

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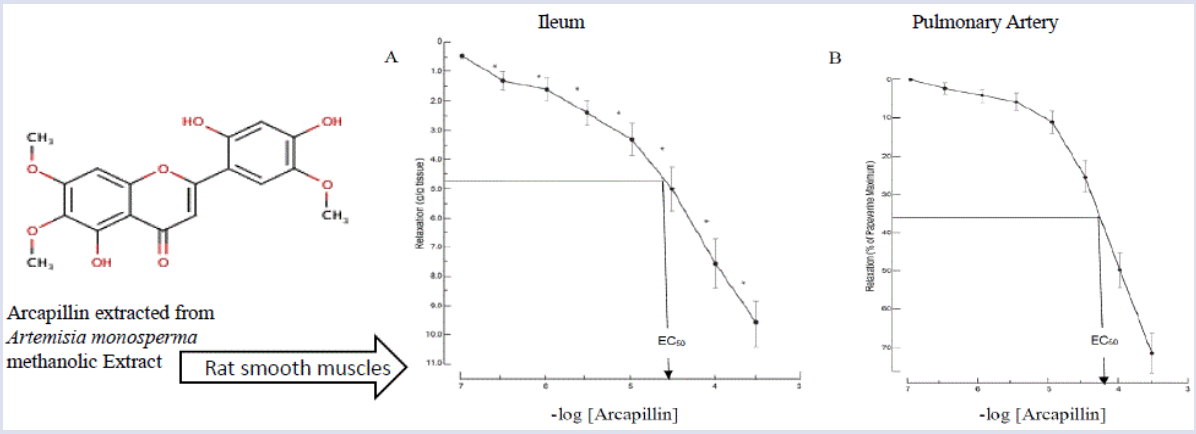
GRAPHICAL ABSTRACT



SUMMARY

- Arcapillin, 2',4',5-trihydroxy-5',6,7–trimethoxyflavone, was isolated for the first time from *A. monosperma*. It seems to contribute to the pharmaceutical importance of *Artemisia* species.
- The effect of arcapillin on smooth muscles was evaluated over eight cumulative concentrations of half log units in the range of [10^{-7} M -3×10^{-4} M].
- Arcapillin showed a concentration-dependent inhibition of ileal smooth muscle contraction with an EC_{50} of 2.8×10^{-5} M.
- The highest concentration of arcapillin tested (3×10^{-4} M) on ileum induced ~65% relaxation compared to the maximum relaxation induced by papaverine. The induced inhibition was reversible within a minute upon washing off the flavone.
- Arcapillin caused a relaxation of the tone of contraction of the pulmonary artery muscle with an EC_{50} of 5.8×10^{-5} M. The highest concentration tested (3×10^{-4} M) induced 70.9% relaxation compared to the maximum relaxation caused by papaverine.
- Arcapillin in a concentration of 3×10^{-5} M slightly increased the contraction of the smooth muscle of the urinary bladder.
- Tracheal smooth muscles were not affected by all tested concentrations of arcapillin.
- The relaxation of ileum induced by arcapillin could be due to decreased availability of cytosolic calcium or due to an increased cAMP via inhibiting the phosphodiesterase enzyme. However, the contractile effect on the urinary bladder muscles could be due to inhibiting the α-adrenergic receptors.
- The precise mechanism of action of arcapillin on smooth muscles should be investigated.

ABOUT AUTHORS

Dr. Lubna Abu-Niaaj is an Assistant Professor of Biology at Central State University, USA. Her molecular studies resulted in the deposition of Xenopus laevis SOCS1 cDNA sequence into the Database of the National Center for Biotechnology Information. Dr. Abu-Niaaj's publications are on muscle physiology, natural products and molecular genetics. Dr. Abu-Niaaj is a reviewer for multiple scientific journals and a member in several professional societies including the Society for Developmental Biology, American Society of Physiology and the American Society for Microbiology.

Dr. Ibrahim Katampe is an Associate Professor of Chemistry and currently the Assistant Director for Innovation & Technology Incubation the College of Engineering, Science, Technology and Agriculture (CESTA), Central State University. Dr. Katampe is a research scientist with research and product development experiences in both academia and the private sectors. His research experiences include but not limited to advanced material synthesis, biological and chemical inhibition chemistries, biopolymers and natural product chemistry, waste water pollution remediation technologies. He is published in several Chemical and allied academic journals and is an inventor with about nine United States issued patents.

Dr. Shtaywy S. Abdalla is a Professor of Biology at the University of Jordan. He held several administrative positions as the provost, vice president for Science and Medical Faculties and others. He also served as the President of the Tafila Technical University. Dr. Abdalla has a Ph.D. in Physiology from the University of Wisconsin (USA). His research focuses on muscle physiology, endocrinology, hematology and inflammation on which he published more than 50 research papers in international journals. He authored and co-authored several books and under his supervision, more than 30 students earned their master's and doctorate degrees.

Cite this article: Abu-Niaaj LF, Katampe I, Abdalla SS. Evaluation of Antispasmodic Effect of Arcapillin on Rat Smooth Muscle. Pharmacog J. 2019;11(4):712-7.