VASORELAXANT AND ANTISPASMODIC EFFECTS OF SOME POLYPHENOLS AND GLYCOSIDE IN RAT SMOOTH MUSCLES

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Abstract:

Objective: The present study was undertaken to investigate the effect of Luteolin, chlorogenic acid, amygdalin and tannic acid on vascular smooth muscle contractility.

Materials and Methods: The effect of different concentrations of some polyphenols and glycosides on contractile responses of isolated aorta, ileum and trachea to Acetylcholine, KCl and phenylephrine (PE) were evaluated.

Results: The results of the current study indicated that luteolin and chlorogenic acid has potent relaxant effects on KCl and PE-induced contractions in rat's aortic ring. Amygdalin and tannic acid reduced ACh-induced ileum contractions significantly. Conclusions: The inhibitory effect of luteolin and chlorogenic acid on the contraction induced by PE and KCl may be due to their anti-adrenergic and anti-hyperpolarizing effect.

Keywords: vasorelaxant, antispasmodic, polyphenol, glycoside, rat, smooth muscles

Introduction

Increasing evidence indicates that regular and moderate consumption of polyphenol-rich beverages or foods may exert protective effects on the cardiovascular system (Leblais *et al.* 2008). Polyphenols represent a superfamily of diverse naturally occurring phytochemicals (Menaa *et al.* 2014).

Flavonols and flavones are plant-derived polyphenolic compounds that are commonly consumed in the diet. Epidemiological studies indicating that high dietary intake of flavonols reduces the risk of cardiovascular disease and subsequest mortality (Graf *et al.* 2005). Luteolin, a flavone which is the major component in many herbal plants, has a variety of pharmacological effects, including antihypertensive (Loizzo *et al.* 2007), anti-inflammatory (Chen *et al.* 2014), and anti-oxidative (Song & Park 2014).

Recently, basic and clinical investigations have implied that the consumption of chlorogenic acid have an anti-hypertensive effect (Zhao *et al.* 2012). Chlorogenic, the ester of caffiec and quinic acida, is a well-known antioxidant agent. Chlorogenic acid plays a major role in the protective effect against ischemia-reperfusion injury (Sato *et al.* 2011) and also may be beneficial for the prevention and treatment of inflammations (Hwang *et al.* 2014).

Amygdalin (vitamin B17, or Laetrile), is extracted from Semen Persicae, the seed of *Prunus persica* (L.), Batsch and other rosaceous plants (Chang *et al.* 2006). Amygdalin is effective at alleviating inflammatory pain and it can be used as an analgesic with anti-nociceptive and anti-inflammatory activities (Hwang *et al.* 2008). Besides the antitumor activity amygdalin has also been used for the treatment of asthma, bronchitis, emphysema, leprosy and diabetes (Baroni *et al.* 2005) and (Hwang *et al.* 2008).

Tannic acid, (TA) a naturally occurring plant polyphenol, is composed of a central glucose molecule reprivatized at its hydroxyl groups with one or more galloyl residues (Gülçin *et al.* 2010). Tannic acid has well-described as an antimutagenic and antioxidant agent (Andrade *et al.* 2005).

However, there is a dearth of information's on the effect of polyphenol and glycoside on the contractility smooth muscle, thus, the present study was designed to investigate the relaxant action of selected polyphenol and glycoside on isolated rat thoracic aorta, ileum and trachea.

MATERIALS AND METHODS

Animals

Adult male albino rats *Rattus rattus* weighting (200-300 g) were used for all experiments, kept in plastic cages and maintained in animal house of the Department of Biology, College of Science, University of Salahaddin. They were kept at 24 C^o and exposed to a photoperiod cycle of 12 hrs light follow by 12 hrs darkness. The had free access to water but food withdrawn 24 hr. prior to the experiments. They were fed standard diet and tap water.

Chemicals and Drugs:

Phenylphrine chloride, Acetylcholine hydrochloride, Luteolin (Roth-Germany), and potassium chloride (BDH - UK). Fresh physiological Krebs and Tyrodes solutions were prepared daily for tissue experiments

Isolated Aorta Preparation and Experimental Protocol

The animals were injected intrapretoneally with heparin (2000 units/ 200 gm) and left for 30 min, to avoid blood clotting and possible damage of endothelium of the aorta(Fulton *et al.* 1996). Animals then anaesthetized with Ketamine (40/kg mg) and Xylazine (10 mg/Kg) intraperitonealy. The chest cavity was opened, and after removal of excess tissue and fat, the isolated aorta was transferred to a beaker containing Krebs solution aerated with 95% O_2 and 5% CO_2. The beaker was placed in the water bath at 37 C^o. The aorta cut into rings approximately 3.5 mm. Only the first four segments distal to the aortic arch were used. Due to an apparent difference in magnitude of contraction resulting from aortic ring after 4^{th} segment.

The procedure of (Shekha & Al-Habib 2012) was followed to study the vascular activity of isolated aorta, ileum and trachea. Briefly, it includes the carful insertion of two stainless steel wires into lumen of the aortic rings, then one wire was anchored to the base of the glass organ bath (High Tech tissue organ bath Radnoti, Model 166051 /2EA) and the other wire was connected to a force transducer (Model MLT0201/RAD 5 mg-25 gm) coupled to the transbridge amplifier (Model ML 224, Quad Bridge Amp) and PowerLab Data Acquisition System (Model ML 870, PowerLab, ADinstrument , Sydney, Australia) and computer running Labchart Pro software (Version 7) was used for measurement of isometric tension.

The organ bath was filled with 10 ml oxygenated (95% O_2 and 5% CO_2) Krebs solution. The temperature of solution inside the tissue bath was maintained 37 C^o by circulating water through water jacket from a circulating water bath set at 37 C^o (Thermo-Fisher Scientific, USA).

Aortic Rings were allowed to equilibrate for 60-90 min at a resting tension of 2 gm with buffer solution changed every 15 minutes. When isometric tension had stabilized, concentration-response curves (CRCs) for acetylcholine $1X10^{-9}$ – 10^{-5} mol/L, submaximal dose of phenylephrine $1X10^{-6}$ M and KCl 60 mM were established.

Ileum Preparation and Experimental Protocol

Rats were anaesthetized, the abdomen was opened, the caecum was lifted forward and the ileo-caecal junction was exported. The ileum was cut at the junction and transferred into a beaker containing Tyrodes solution at 37 C^o. Segments of ileum (2 cm in length) were mounted in the 25 ml tissue bath and under 1 g tension.

One end of the segment was attached to a glass tissue hook and the other end was attached by cotton thread to a force transducer coupled to a transbridge and PowerLab Data Acquisition System (Australia, ADInstruments) connected to a computer running Labchart software (Version 7) for measurement of isometric tension.

A pre-load of 1 gm was applied to each tissue and kept constant through the experiments. The tissue was washed several times within 5 min. interval and allowed to equilibrate for 30 min., before recording the isometric contractions by submaximal concentration ACh induction. An agonist constant time 20 seconds was used together within 3 minutes interval between doses once the tissue was stabilized with reproducible effects from the doses of standard. The volumes used were usually not exceeding 5% of bath volume. Test materials were then added in a cumulative pattern was to obtain concentration-dependent inhibitory responses (Van Rossum, 1963). The relaxation of ileum preparation, pre-contracted with high ACh 10 uM was expressed as percent of the control response mediated by ACh.

Isolated Trachea Preparation and Experimental Protocol

The trachea was removed, cleaned and 5 rings (each containing 3-4 cartilaginous ring segments) were obtained from distal region of the trachea. The tissue was suspended on two stainless steel wires in 10 ml organ bath containing Krebs solution at 37 C^o under isometric tension of 1 gm. The preparation was allowed to equilibrate for at least 1 hr before the addition of any drug, while, it was washed with buffer solution every 15 min, the pH of the buffer was maintained at 7.4 by continuous aeration of the organ bath with a gas mixture contain 95% O_2 and 5% CO_2.

In some preparations, ACh (10 uM) was used to stabilize the respective preparations until constant responses of each agonist were produced. After obtaining sustained contractions, the relaxant effect of the test materials were assessed by adding in a cumulative fashion. Cumulative dose-response curves for ACh were constructed using different concentrations of agonist. When a 3-fold increase in concentration produced no further increment in response, the tissue was washed to re-establish the base-line tension. Isometric responses were recorded using force transducer coupled to the transbridge and Power Lab Data Acquisition System and computer running Labchart software for measuring isometric tension. Inhibition of contraction of the tracheal ring was expressed as a percentage of the maximum contraction.

Statistical analysis

Data are presented as Means ± SEM. The statistical analysis was performed using one way analysis of variance (ANOVA) followed by Dunnett test. P-value less than 0.05 ($P<0.05$) was considered as statistically significant. The Log IC_{50}s values (i.e., the concentration of the agonist or extract that produced 50% reduction of maximal relaxant responses) were determined from the concentration–response curves by non-linear regression analysis using GraphPad Prism™ software, version 6 (GraphPad Software, Inc., San Diego, CA, USA).

RESULTS

Dose–response curves of luteolin in PE- and KCl-Contracted Thoracic Aortic rings

Dose–response curve of the effect of luteolin against KCl and PE-induced contractions in aortic rings are shown in Fig (1 and 2). Luteolin at a concentrations from $2X10^{-4}$ – $4X10^{-4}$ M caused a highly significant ($P<0.001$) relaxant effect on KCl precontracted rat thoracic aortic rings. Luteolin also produced significant relaxed effect on PE 10 uM induced contraction in aortic rings $2X10^{-4}$ ($P<0.05$) and $3X10^{-4}$ – $4X10^{-4}$ M ($P<0.001$).

The Log IC_{50}±SE, (Log IC_{50} of CI 95%) and E-Max % of maximum contraction (E-Max) are shown in Table 1. Luteolin showed more potent inhibitory effect on KCl than PE-induced contractions in aorta. For KCl and PE precontracted aorta, Log IC50's± SE (Log IC50 of CI 95%) were -3.635± 0.01655 (-3.669 to -3.602) and -3.620±0.0252 (-3.672 to -3.569), whereas E-Max% values were 101.8 % and 99.09 %, respectively.

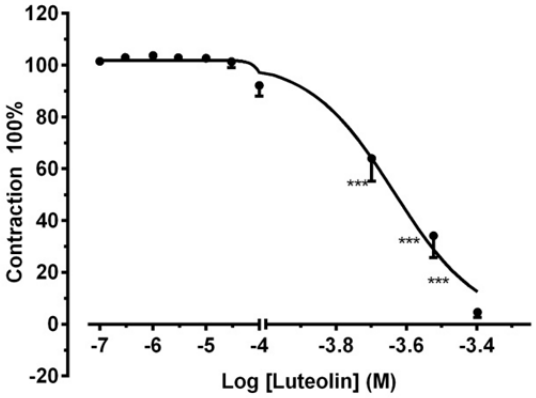

Fig 1. Cumulative dose-response curve for the effects of Luteolin on KCl (60mM) induced contractions in rats aorta. *** represents P<0.0001.

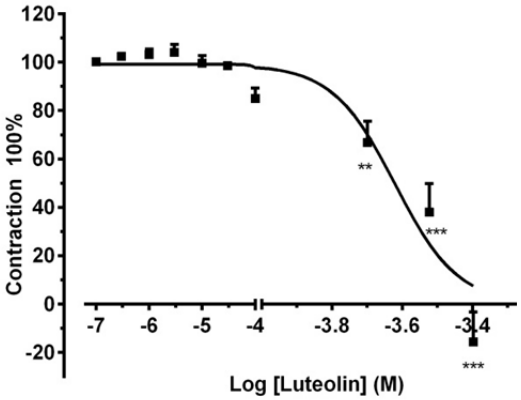

Fig 2. Cumulative dose-response curve for the effects of Luteolin on PE (10 uM) induced contractions in rats aorta.*, ** and *** represent P< 0.05, P< 0.01 and P<0.001, respectively.

Dose–response curves of Chlorogenic Acid in PE- and KCl-Contracted Thoracic Aortic rings

Dose–response curve of the effect of chlorogenic acid against KCl and PE-induced contractions are shown in Fig (3 and 4). Chlorogenic acid at concentrations $4.5X10^{-4}$ – $5X10^{-4}$ caused a significant ($P<0.01$) relaxant effect on KCl 60 mM precontracted rat's thoracic aorta. Chlorogenic acid also produced significant relaxant effect on PE 10uM induced contraction in aortic rings $3X10^{-4}$ ($P<0.05$) and $3.5X10^{-4}$ – $5X10^{-4}$ M ($P<0.001$).

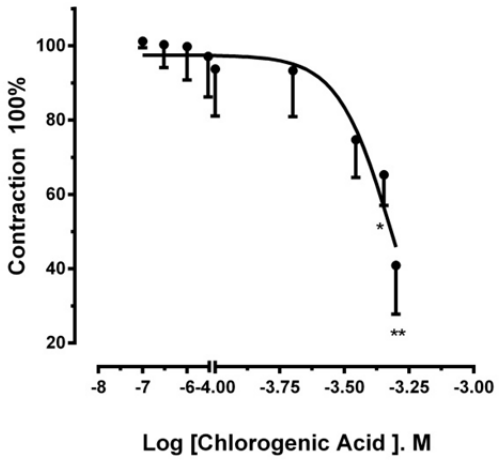

Fig 3. Cumulative dose-response curve for the effects of Chlorogenic acid on KCl (60mM) induced contractions in rats aortic ring. * and ** represent P<0.05 and P< 0.001, respectively.

The Log IC_{50}± SE, (Log IC_{50} of CI 95%) and E-Max % are shown in Table 1. Chlorogenic acid showed inhibitory effect on KCl and PE-induced contractions in aorta. For KCl and PE precontracted aorta, Log IC50's± SE (Log IC50 of CI 95%) were -3.314±0.03266 (-3.380 to -3.247) and -3.466±0.007871 (-3.482 to -3.450), whereas E-Max% values were 97.48 % and 106.4%, respectively.

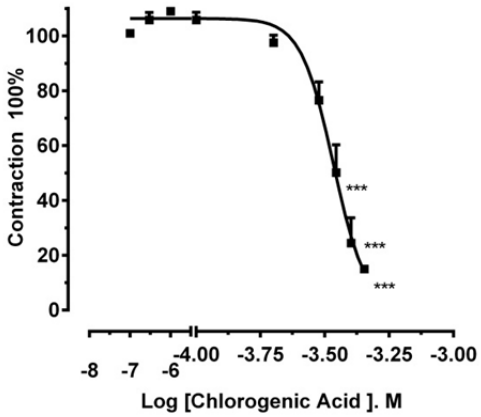

Fig 4. Cumulative dose-response curve for the effects of Chlorogenic acid on PE (10 uM) induced contractions in rats aortic rings. *** represents P<0.0001

Dose–response curves of Amygdalin and Tannic Acid in PE-Contracted Thoracic Aortic rings

Dose–response curve of the effect of Amygdalin and Tannic acid against PE-induced contractions are shown in Fig (5 and 6). Amygdalin and Tannic Acid produced non-significant effect on PE-induced contraction in aortic rings. The Log IC50± SE, (Log IC_{50} of CI 95%) and E-Max % are shown in Table 1.

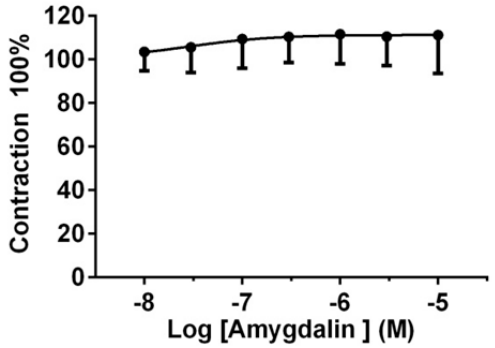

Fig 5. Cumulative dose-response curve for the effects of Amygdalin on PE (10 uM) induced contractions in rats aortic rings.

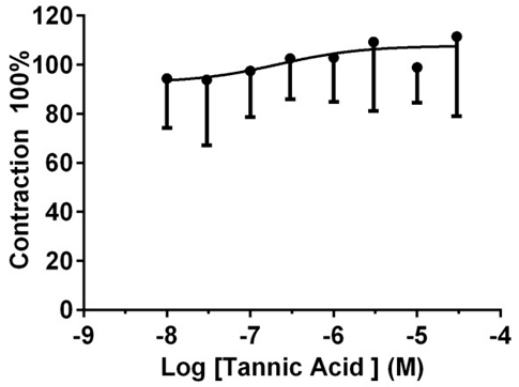

Fig 6. Cumulative dose-response curve for the effects of Tannic acid on PE (10 uM) induced contractions in rats aorta.

Dose–response curve of Amygdalin and Tannic Acid in ACh-Contracted Rat Ileum

Dose–response curve of the effect of Amygdalin and Tannic acid against on ACh-induced ileal contractions are shown in Figures (7 and 8). Amygdalin at (3 X 10^{-2} M), (1.8X10^{-2}-1X10^{-2} M) and (6.7X10^{-3}- 4X10^{-3} M) caused a significant relaxation in the ACh (10 uM) precontracted ileum of the rat at level (P<0.001), (P<0.01) and (P<0.05) respectively.

Tannic acid at concentrations 3X10^{-4}-3X10^{-7} M caused a highly significant relaxation (P<0.001), whereas at 1X10^{-7} M, it caused just a significant (P<0.05) relaxation in the ACh (10 uM) precontracted trachea of the rat.

The Log IC_{50}± SE, (Log IC_{50} of CI 95%) and E-Max % are shown in Table 1. The Amygdalin and Tannic acid produced inhibitory effect on ACh- induced contractions, with a (Log IC50± SE) of -5.547±0.1742 M/mL and -5.421±0.2429,

(with a Log IC50 of CI 95% between -5.923 to -5.171 and -5.926 to -4.916) and E-Max of 63.89% and 68.87% respectively.

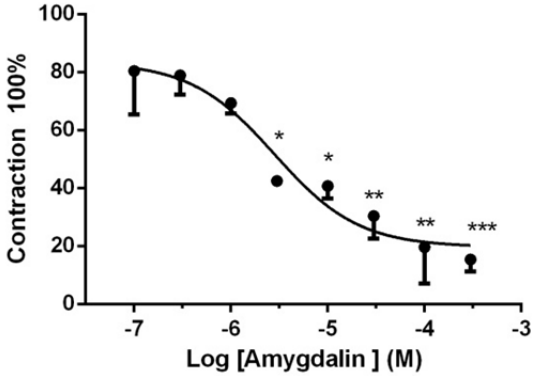

Fig 7. A cumulative dose-response curve for the effect of Amygdalin on ACh (10 uM) induced contraction in rats ileum. *** represents P<0.0001, ** represents P<0.001 and *represents P<.0.05.

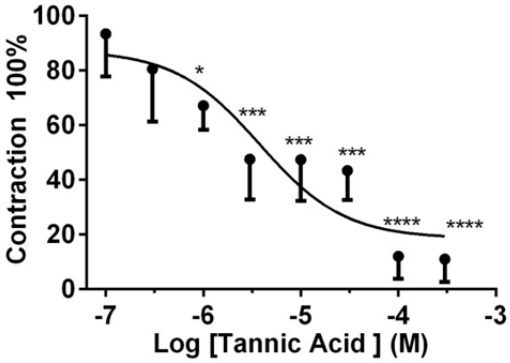

Fig 8. A cumulative dose-response curve for the effect of Tannic acid on ACh (10 uM) induced contraction in rats ileum. *** represents P<0.0001 and *represents P<.0.05.

Dose–response curve of Amygdalin and Tannic Acid in ACh-Contracted Rat trachea

Dose–response curve of the effect of Amygdalin and Tannic acid against PE-induced tracheal contractions are shown in Fig (9 and 10). Both amygdalin and tannic acid produced non-significant effect on ACh (10 uM) precontracted trachea of the rat. The Log IC50± SE, (Log IC_{50} of CI 95%) and E-Max % for amygdalin and tannic acid are shown in Table 1.

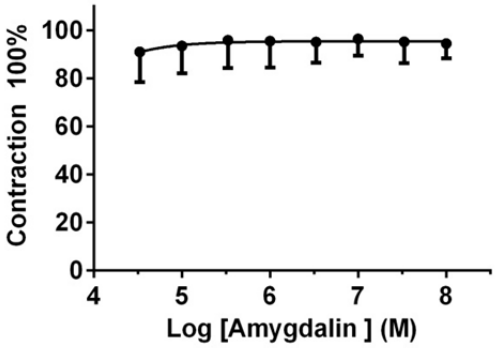

Fig. 9 . Cumulative dose-response curves for the effect of Amygdalin on ACh (10 uM) induced contractions in rats tracheal ring.

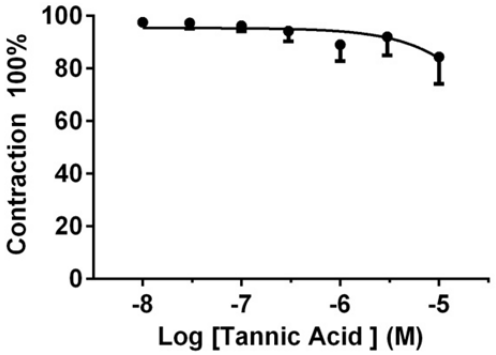

Fig. 10. Cumulative dose-response curves for the effect of Tannic acid on ACh (10 uM) induced contractions in tracheal rings

Discussion

The present study indicated that luteolin and chlorogenic acid have potent relaxant effect on KCl and PE-induced contractions on rat's aortic ring. PE is a selective alpha 1- adrenergic receptor agonist and induced an initial transient phasic contraction followed by a tonic contraction (Shi *et al.* 2006). The initial contraction is mediated by intracellular Ca^{++} release, whilst the sustained tonic contractions resulted from Ca^{++} influx via the receptor-operated Ca^{++} channels through activation of G-protein and activates Phospholipase C (PLC) which elevate Ininisitol triphosphate and Ca^{++} (Karaki & Weiss 1988).

It is well known that KCl induces smooth muscle contraction through activation of voltage gated calcium channels (VGCs) and subsequent release of Ca^{++} from the sarcoplasmic reticulum, without influencing other signal transduction systems such as phosphatidylinositol turnover and Ca^{++} sensitization (Kumar *et al.* 2008).

The relaxant effect of Luteolin on isolated tissue preparations used during the present work may be partially due to the inhibition of protein kinase C. Inhibition of cyclic nucleotide phosphodiesterases (PDE) or decreased Ca^{++}uptake may also contribute to their vasodilatory (Duarte *et al.* 1993).

The mechanisms of relaxant action of luteolin in the current study are similar to those of (Ko *et al.* 2005) and his coworker. They stated that luteolin had antispasmolytic activity in isolated guinea pig trachea, which may be due to its inhibitory effects on both PDE activities and the subsequent reduction in $[Ca^{++}]_i$ of the trachealis(Ko *et al.* 2005).

In thoracic aorta, the chlorogenic acid also produced dose-dependent inhibiting effect on contractions induced by PE and high K^+ in isolated thoracic aorta. It is difficult to compare the results since the current study represents a first attempt to study the effect of chlorogenic acid on KCl and PE precontracted aorta rats. However, (Bankar *et al.* 2011) found the vasorelaxant and antihypertensive effects of *Cocos nucifera Linn*, (rich in chlorogenic acid) via nitric oxide production in a concentration and endothelium-dependent manner This effect may due to direct activation of nitric oxide / guanylate cyclase pathway, stimulation of muscarinic receptors and/or via cyclo-oxygenase pathway.

Amygdalin and tannic acid showed a non-significant effect on aorta and trachea while have a significant effect on ileum rats. Since no attempt have been made so far to study the effect of amygdalin and tannic on rat ileum, trachea and thoracic aorta pretreatment with ACh and PE it is in almost impossible to compare the results.

Amygdalin and tannic acid inhibited the ACh (10 μM) induced contraction in a concentration dependent fashion in rat's ileum. ACh is a neurotransmitter that activates muscarinic receptor located in the plasma membrane of smooth muscle cells and bind with M_3 receptor (Chung 2008). After binding of ACh with its receptor, it activates G-protein ($G_{q/p}$) and activates PLC.

The PLC cleaves PIP2 into diacyle glycerol (DAG) and IP3. IP3 IP3 releases Ca2+ from the endoplasmic reticulum (ER), and DAG activates PKC (Chung 2008). ACh caused depolarization and tonic contraction of intestinal and tracheal smooth muscle (Chung 2008).

Activation of muscarinic receptors of longitudinal smooth muscle of rat's ileum and trachea increased the frequency of action potential and rising rate of depolarization which results in smooth muscle contraction (Reddy *et al.* 1995). The ACh-evoked contraction is generally considered as mediated via M3 muscarinic receptor. Furthermore, the preponderance of M2 subtype muscarinic binding sites may contribute in ACh induces contraction (Fatehi *et al.* 2004).

In ileum, the amygdalin and tannic acid may act through blocking the muscarinic receptors. The anti-contractility effect of the amygdalin and tannic acid on rat ileum may be due to inhibit either non-selective cation channels in the plasma membrane, which results in membrane depolarization or inhibits activation of the release of intracellular Ca^{++}. Change in the membrane potential stimulates Ca^{++} influx through VGCs (Namkung *et al.* 2010). However, (Calixto *et al.* 1986) showed that tannic acid can affect Ca^+ availability for contraction of smooth and cardiac muscles. This action could well mask the effects of other active constituents of tannic-rich plant extracts (Habauzit & Morand 2012).

In conclusion, this summary of existing scientific evidence indicates that inhibitory effect of luteolin and chlorogenic acid on the contraction induced by PE and KCl may be due to their anti-adrenergic and anti-hyperpolarizing effect.

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پوختە:

مەبەست: ئەم توێژینەوە ئەنجام درا بۆ دیارکردنی کاریگەری لیتیولین وترشی کلۆرۆجینینك وئەمێگدالین وترشی تانیك لەسەر گرژبوونی ماسولکەی لووس لە بۆری خوێن.

پێداویستی وشێوازی کارکردن: هەلسەنگاندنی کاریگەری خستی هەمەجۆر لە پۆلی فینۆل و گلایکۆساید لەسەر گرژبوونی شاخوێنبەر لە جورج. ریخۆلە و بۆری هەوا بە رێگای ئەسیتایل کۆلین و کلۆریدی پۆتاسیوم و فینایل فرین.

ئەنجام: ئەنجامی ئەم لێکۆلینەوەیە دەرکەوت لیتیولین وترشی کلۆرۆجینیك کاریگەری خاوبونی هەیە لەسەر شاخوێنبەری جورج کە گرژکرا بە PE. کە چی ئەمێگدالین و ترشی تانیك کاریگەری زۆر بەهێزی هەبوو لەسەر ریخۆلە گرژکراو بە ACh.

دەرئەنجام: کاریگەری رێگرتن لیتیولین و ترشی کلۆرلۆجینیك لەسەر ئەو گرژبوونەی بۆ هوی PE و KCI وە لەوانەشە کاریگەریەکە دژە ئەرینالینی و دژە هایپەرپۆلەریاز بێت.

الخلاصة:

الهدف: اجريت هذه الدراسة للتعرف على اثر ليتيولين وحمض الكلوروجينيك و أميغدالين وحمض التانيك على انقباض العضلات الملساء في الأوعية الدموية.

المواد و طرق العمل: تم تقييم تأثير التراكيز المختلفة من بعض البوليفينول وجليكوسيدات على الاستجابات الانقباضي من الشريان الابهر المعزول، الدقاق والقصبة الهوائية بواسطة أستيل كولين، كلوريد البوتاسيوم وفينايل فرين

النتائج: أظهرت نتائج الدراسة الحالية أن ليتيولين وحمض الكلوروجينيك لها تأثيرات ارتخائية قوية المتقلصة بواسطة PE في حلقة الشربان الأبهر للفئران. أميغدالين وحمض التانيك خفضت تقلصات الدقاق معنويا بواسطة ACh

الاستنتاجات: إن تأثير كابح من ليتيولين وحمض الكلوروجينيك على الانكماش الناجم عن PE و KCl وقد يكون السبب تأثير ضد الأدرينالية و ضد فرط القطبية.