Ex-vivo abortifacient activity of *Androsace foliosa n*-hexane leaves extract on isolated rabbit uterus

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Abstract: *Androsace foliosa* is a medicinal herb utilized in different areas of Pakistan for abortifacient, diabetic and liver complications. In the current research, the possible action of the *n*-hexane leaves extract of the *Androsace foliosa* on isolated rabbit uterus was examined. Abortifacient activity was examined in the existence of standard antagonist e.g. atropine and salbutamol and a uterine tonic like oxytocin. The isolated rabbit uterus is initially treated with 1mg/kg stilboesterol for 1 complete day. The consequence of oxytocin as uterine contraction agonist was observed. Additionally, antagonists e.g. salbutamol (2µg) and atropine (1-2mg) on the uterine contractile action of the extract were also examined. The *A. foliosa n*-hexane leaves extract fashion dose correlated amplification in the force of uterine contraction comparable to oxytocin. The drug oxytocin was pragmatic to amplify the uterine contractile action of the extract. Meanwhile pre-treating the tissue with either atropine or salbutamol earlier than administrating the extract indicates the inhibitory action of the drugs on the action of the extract.

Keywords: *Androsace foliosa*, uterine contraction, oxytocin, atropine, salbutamol, prostaglandin.

INTRODUCTION

Fertility management is a noteworthy subject of universal and nationalized community health distress. Population burst is the forth coming obstacle for the Country's development as the natural resources are inadequate. Ever increasing human population has damaging effects on all features of development predominantly environment, health care, employment and education (Adebisi and Alebiosu, 2014). Rapid increase in population has triggered adverse effects in the economic advancement and entire encircling human growth leading to poverty in developing countries. Fertility regulation, including contraception and management of infertility forms a significant section of reproductive health (Wikhe *et al.,* 2013). Delivery Control also branded as contraception and fertility management is techniques or devices utilized to stop pregnancy. Global exploration on anti-fertility agents is to challenge the problem of population outburst (Adebisi and Alebiosu., 2014). Herbal drugs involve the use of whole plant or parts of plant used to stop and treat illnesses and to sustain physical condition and curing. Herbal medicines are the oldest variety of drugs recognized to man (Boer and Cotingting, 2014). Abortion essentially refers to premature ejection of human fetus. Abortion is either naturally unprompted (miscarriage) or unnaturally induced e.g. surgical abortion (Das *et al.,* 2014). The abortifacient is a substance that induces abortion. Countless herbal remedies are conventionally used as contraceptives (to control ovulation) and abortifacient (to stop implantation). Furthermore herbal medicines are also emmenagogues (to avoid uterine flow) and oxytocic's (to stimulate uterine tightening, predominantly to induce labor) (Feroche., 2015). Countless herbs have been reported used historically by women to aid child delivery, stimulate menstrual flow or reduce fertility. Anti-fertility herbs directly affect pituitary gland via blockage of luteinizing (LH) and follicle stimulating hormone (FSH) (Patel *et al*., 2015). Synthetic drugs are associated with severe side effects e.g. gastro-intestinal troubles, systemic illness, sterility, rigorous painful uterine contraction and fatality. Numerous investigations for introduction of anti-fertility affect have been investigated counting hormonal, chemical and immunological interventions (Dabhadkar *et al*., 2015). Abortifacient pills including hormonal and synthetic steroids possess many side effects such as high bleeding, nausea, headache, diarrhea, cramping, abdominal pain and sepsis. The synthetic hormonal contraceptives cannot be used continuously because of their side effects e.g. dyspepsia, depression, weight gain, hyper-menorrhea and

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hemorrhage (Yakubu *et al.,* 2010). Contraceptives use before a surgical procedure can increase the risk of postsurgical thromboembolism, cerebral embolism and myocardial infarction. To avoid the inevitable advanced effects of drugs prepared from chemical sources, indigenous plants are given preference, which are also cheap, easily available and harmless (Sathya *et al.,* 2014). Consequently scientists investigated for self-administrable, low cost, fewer derivatives with minor side effects and with absolute reversibility.

Furthermore countless native plants prevent the birth, a small number of plants have been investigated for their anti-fertility action. Ethno-pharmacological knowledge helps to segregate safer and economical active compounds from plants than separating active compounds from plants with no record of human use (Tsewang, 2016). Thus, current study was performed on plant *Androsace foliosa* which is used locally for abortifacient purposes by local people of Pakistan. *Androsace foliosa* syn. *Androsace sarmentosa* (Primulaceae) is found in India and Pakistan. Leaves are used for correcting menstrual flow, and helps in avoiding conception. *Androsace foliosa* is also used to cure amenorrhea, skin allergies, leucorrhoea and as abortifacient (Bose *et al*., 2014). Nevertheless, effect of this plant on reproductive system is not conducted scientifically to authenticate its ethno-botanical use. Thus, in the current study, the feasible action of *n*-hexane extract of *Androsace foliosa* leaves on isolated rabbit uterus was examined. Effect of this fraction on rabbit uterus in the presence of standard antagonists e.g. atropine and salbutamol and uterine stimulant like oxytocin were investigated.

MATERIALS AND METHODS

Plant material

The plant *Androsace foliosa* was collected from Donga Gale, Ayyubia National Park Pakistan in July 2014. The plant was identified by a Botanist Dr Ajmal, University of Poonch, Rawlakot. The specimen was kept in herbarium of Botany Dept. G.P.G.C # 1. Voucher number was 5636. After washing carefully with tap water to remove dirt etc the plant was shade dried. After drying plant was chopped and reduced to fine powder. Plant in the form of fine powder was kept in air tight container.

Preparation of extract

Shade drying method was selected for drying of leaves of *Androsace foliosa.* After drying the leaves were pulverized with the help of electric grinder. Afterwards extraction was performed using the process of maceration. *Androsace foliosa* leaves powder (500 grams) was soaked in n-hexane (1500 ml) for total of 7 days. The mixture was shaken intermittently. The blend was filtered with the help of muslin cloth followed by using Whattman filter paper (No.1). The resultant filtrate was evaporated to dryness with the help of rotary evaporator at 50 degree and under decreased pressure. After dryness the fraction provide a yield of 11 percent (w/w).

Animals

Virgin female rabbit weight (1-2 kg) was used for the study. The animals were reserved in well-ventilated room with standard housing circumstances with 12 hour dark/ light phase. Animal center organization of Pharmacy and Technology laboratory Abbottabad was the facility where animals were kept. They had excess to regular diet and un-limited excess to water. The animals were fasted 24 hours before the experiment. The research was performed with appropriate authorization by organization Animal Ethics board. Experiments were conducted according to the modern guiding principle for the concern of laboratory animals.

Drugs and chemicals

Atropine and Salbutamol (GSK as gift sample), Stilboesterol and oxytocin (Abbott as gift sample), D-glucose, potassium hydrogen phosphate, MgSo4 (Heptahydrate), $CaCl_2$dehydrate; Nacl, sodium hydrogen carbonate and KCl were used in this testing. All the chemicals were obtained from Merck Germany.

Dose of standard drug and plant extract

Effect of both oxytocin and *n*-hexane leaves extract of *Androsace foliosa* was examined on isolated rabbit uterus. Comparison of oxytocin (control) and various doses of *n*-hexane leaves extract of *A. foliosa* were carried out. Oxytocin was given at the dose of 0.16i.u to check uterine force of contraction. *Androsace foliosa* *n*-hexane leaves extract was given at the dose of 0.01, 0.03mg/mL, 0.1, 0.3, 1, 3, 5 and 10mg/mL, respectively.

Isolated organ preparations

To achieve the estrogenized uterus, the rabbits were administered with stilboesterol 1mg/kg S/C 24 hours prior to starting the research. The rabbits were dissected by cervical dislocation. After opening peritoneal cavity, uterine horns were detached and get rid from fatty and connective tissue. Longitudinal myometrium strips measuring 0.5 to 10 mm were cut off. To quantify force, uterine strips were attached to every end of metal hooks. The uppermost hook was attached to transducer and 1g was the resting tension provided to tissue. The tissue was kept in bath possessing De Jalon's physiological solution at 37°C. Furthermore, the tissues were aerated with carbogen (5 % CO_2 and 95% O_2) and 7.4 was the pH maintained. Composition of De Jalon's physiological solution in (g/ml) was (NaCl 9.0 g, KCl 0.42 g, $NaHCO_3$ 0.5g, glucose 0.5g, $MgCl_2$ 0.0006 and $CaCl_2.2H_2O$ 0.08) (Goncalves and Ogava., 2014). The strips were permitted to equilibrate natural contraction. Subsequent to generating stable contractile activity for minimum period (30 minutes) the drug and *n*-hexane leaves extract of

Androsace foliosa were applied through superfusate. The electrical indicator from transducer was enlarged and transformed to digital sign and documented on computer utilizing Chart software.

Drug challenges

After equilibrium stage (30 minutes) uterine contractile responses were elicited by totaling Oxytocin at doses of 0.02-0.16 i.u /mL and *A. foliosa* (n-hexane leaves extract of 0.01-10mg/mL) to the De Jalon's mixture. Contraction amplitude was recorded, after every dose of drug was permitted to operate for 10 minutes. Isotonic transducer was used to record the contraction which is linked to a particular control recorder. The transducer was calibrated to verify alteration in the tension produced on (cm × g) displacement origin and 0.71 tension applied to the preparation. Changes in isotonic tension was documented and confirmed all the way through strength Transducer (MLT-0201), attached with a link Amplifier (N12128) and control Lab (ML 846) figs. Acquisition method (AD Instruments Sydney, Australia). Salbutamol (2 µg) and Atropine (2mg) were used in a dose dependent approach to antagonize the maximal reaction of the cut off uterus to *n*-hexane leaves extract of *A. foliosa* (0.01-10mg) and Oxytocin (0.02-0.16 i.u/ml) 10 minute before addition of standard agonist (Oxytocin) and *n*-hexane leaves extract of *A. foliosa* (Thanamool *et al*., 2013). Data analysis was performed using standard statistical tests.

STATISTICAL ANALYSIS

Data was produced as mean ± standard deviation (S.D) for number of 3 readings. The uterine contractile readings for *A. foliosa*, oxytocin and their mixture were recorded against control readings. These three readings were tested against natural uterine contraction in the absence of any drug) using student T-test. Meanwhile the antagonistic action of salbutamol and atropine was estimated with the analogous interpretation of *A. foliosa* alone by paired T-test.

RESULTS

Both oxytocin and n-hexane leaves extract of *Androsace foliosa* provoke dose correlated amplification in strength of tightening of isolated rabbit uterus (fig. 1). Adding together varying doses of oxytocin to the tissue results in uterine tightening in a dose dependant manner. Comparison of oxytocin (control) and various doses of *n*-hexane leaves extract of *A. foliosa* were carried out. Oxytocin at the dose of 0.16 i.u produced uterine force of contraction (1.5±0.1 g), while *A.foliosa n*-hexane leaves extract showed dose dependent increase in the uterine force of contraction. Results indicates that *A.foliosa n*-hexane leaves extract produced uterine force of contraction of 0.1, 0.2, 0.4, 0.6, 0.8, 1.0, 1.1 and 1.2 g at the dose of 0.01, 0.03 mg/mL, 0.1, 0.3, 1, 3, 5 and 10mg/mL, respectively. Hence uterine contractile outcome created by 10mg of *A. foliosa n*-hexane leaves extract was observed to be very comparable in extent to that as shown by 0.16 I.U of oxytocin. There is increasing uterine force of contraction with each increasing dose. Control (oxytocin) produced uterine force of contraction (1.5±0.1 g) at the dose of 0.16 i.u. Additionally *A. foliosa n*-hexane leaves extract produced contraction (1.2±0.1g) at the dose of 10 mg which is comparable to that of oxytocin (fig. 1).

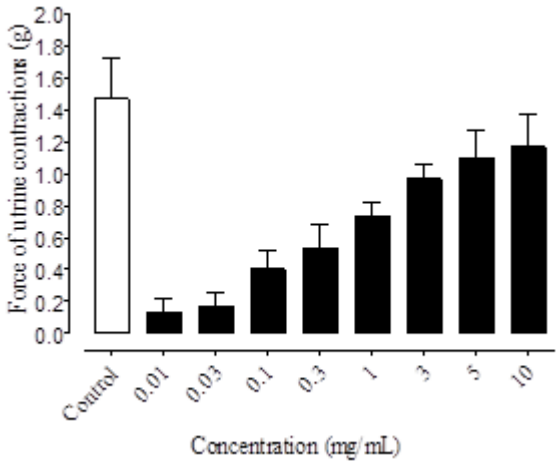

Fig. 1: Relationship of oxytocin (control) and diverse doses of *A. foliosa (n*-hexane leaves extract) on uterine contraction. Values are mean ± S.E (N=6). p< 0.01.

Oxytocin alone produced uterine force of contraction (1.6 ±0.2g). Simultaneous administration of *A. foliosa n*-hexane leaves extract and oxytocin markedly increase the uterine force of contraction. Maximum uterine force of contraction was observed with *A. foliosa n*-hexane leaves extract (5mg/mL) and oxytocin (0.16I.U) simultaneously. Uterine force of contraction of oxytocin and *A. foliosa n*-hexane leaves extract (5mg/mL) was (2.7±0.2g). Uterine force of contraction increased with simultaneous administration of *A. foliosa n*-hexane leaves extract and oxytocin in a linear and dose dependent manner. Moreover, simultaneous administration of oxytocin and *A. foliosa n*-hexane leaves extract shaped uterine force of contraction extensively elevated than either Oxytocin or *A. foliosa n*-hexane leaves extract alone. Result shows that *A. foliosa n*-hexane leaves extract potentiated the uterine contractile effect of oxytocin. Potentiation effect was observed with simultaneous administration of oxytocin and *A. foliosa n*-hexane leaves extract (fig. 2).

Salbutamol was pragmatic to illustrate noteworthy inhibition of uterine contraction obtain by *A. foliosa n*-hexane leaves extract. Results indicates that *A. foliosa n*-hexane leaves extract at the dose of 5mg/mL produced uterine force of contraction of 1.2±0.1g and 1.3±0.1 g at the dose of 10 mg/ ml. Addition of 2µg salbutamol before cumulative dosing of the *A. foliosa n*-hexane leaves

extract produced no contraction at initial doses. Meanwhile this fraction at the dose of 10.0mg/mL indicates uterine contraction (fig. 3).

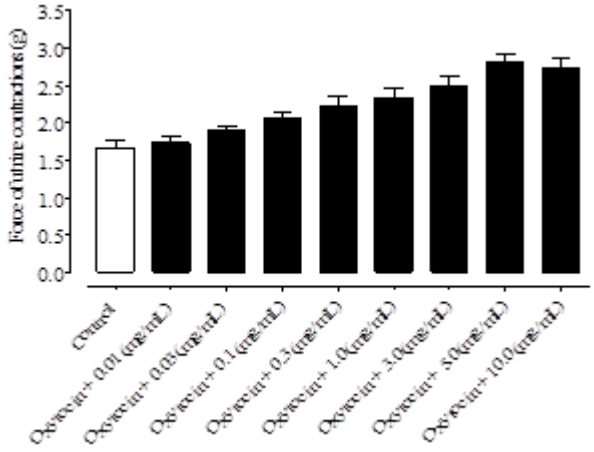

Fig. 2: Synchronized administration of oxytocin and A. foliosa n-hexane leaves fraction. Values are presented as mean ± S.E (N=6) P<0.01.

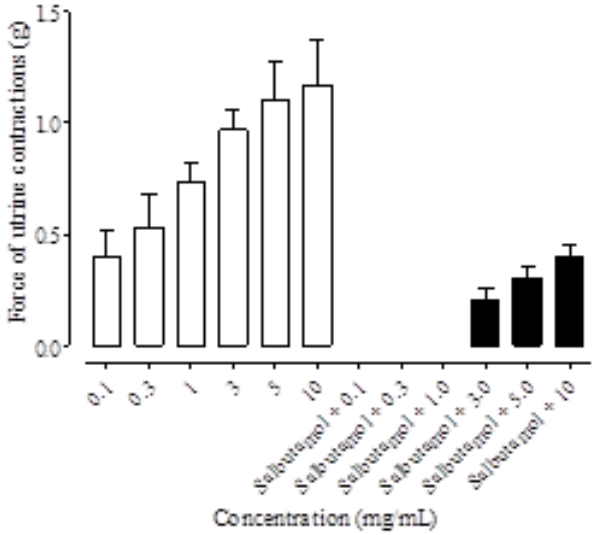

Fig. 3: Inhibitory result of salbutamol on uterine contraction at a range of doses of *n*-hexane leaves extract of *A. foliosa*. Values are presented as mean ± S.E (N=6) P< 0.01.

Adding together atropine did not suggest any consequence on the action of uterus but drastically withdraw the contractile activity of the uterus in a competitive and dose-dependent behavior. Results indicates that *A. foliosa n*-hexane leaves extract when administrated in the absence of atropine produced uterine power of contraction of 1.1±0.25 g at the dose (5mg/mL) and 1.2±0.25 g at the dose of 10mg/ml. Pre-treating the tissues with 2 mg atropine reduces the uterine tightening of 1.2±0.25 g elicited by 3mg of the *A. foliosa n*-hexane leaves extract to 0.5±0.01 g and decreased uterine contraction of 1.1±0.25 g elicited by 10 mg of *A. foliosa n*-hexane leaves extract to 0.4±0.01g. Introduction of 2 mg of atropine entirely block the contraction stimulated by 0.1mg /mL to 0.3mg/mL concentration of the *A. foliosa n*-hexane leaves extract. Contraction induced by 1 mg/mL of the *A. foliosa n*-hexane leaves extract was also extensively introverted by 2 mg atropine (fig. 4).

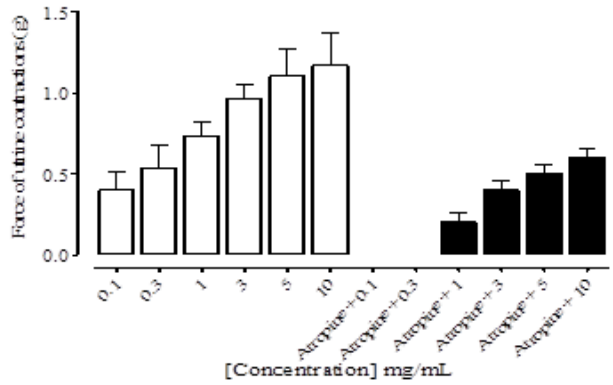

Fig. 4: Inhibitory effect of atropine on uterine contraction of a variety of doses of *A. foliosa n*-hexane leaves extract. Values are calculated as mean ± S.E (N=6) p< 0.01.

DISCUSSION

Birth control is an incredible concern worldwide and physical distress to the public. Rapid increase in inhabitants has triggered solemn harms in the financial progress and individual development leading to poverty in developing countries. Fertility regulation, including contraception and management of infertility forms a significant section of reproductive health (Motsumoto *et al*., 2005). The outcome of the study demonstrated that *A. foliosa n*- hexane leaves extract possess powerful tocolytic action on rabbit myometrium. The extract may possibly restrain spontaneous oxytocin-induced and KCl induced tightening. This extract probably slows down force when merely intracellular Ca supplies (sarcoplasmic reticulum) were available. Consequently this extract is a powerful uterine relaxant performing through several mechanisms. Mechanisms include inhibition of Ca entrance and blockage of Ca discharge from the interior store.

Contraction of the uterine strips to elevated K solution results in increased in intra-cellular Ca concentration. Rise in Ca level results in membrane potential depolarization and therefore leads to contraction. Few Ca channel antagonists can eliminate the K-induced contraction (Disalvo *et al*., 1993). Application of *A. foliosa n*-hexane leaves extract declined the uterine contraction in the presence of high K solution (see fig. 2).

Extract (*n*-hexane leaves) of *Androsace foliosa* has the capability to lower down the excess Ca when the channel is in open form. The existing model of Ca sensitization in smooth muscle contraction is linked with G-protein attached receptors. Elevated K solution can produce contraction by pairing with GPCR. Furthermore, relaxant agents can create the contradictory effects to produce Ca desensitization (Duarte *et al*., 1994). When the uterine strips were incubated with *A. foliosa n*-hexane leaves extract and consequently elevated K solution simultaneously. The uterine strips could not generate force as much as induced by high K only. Our finding also showed that *A. foliosa n*-hexane leaves extract may create Ca desensitization.

Outcome of the current research revealed oxytocin like activities of *n*-hexane leaves extract of *A. foliosa* in the estrogenized isolated rabbit uterus. The extract exerts a concentration dependent elevation in tightening of isolated rabbit uterus. Concentration dependent inhibitory action of salbutamol and atropine on the utmost contractile response was also examined. This inhibitory activity of these antagonists on isolated estrogenized rabbit uterus to the *A. foliosa* (*n*-hexane leaves extract (0.001 -10 mg) were also examined.

The mainly imperative neurohypophysical mammalian hormone is Oxytocin that functions predominantly as a neurotransmitter in the brain. Oxytocin plays a fundamental function in sexual reproduction especially before and following childbirth. It is released in huge quantity after distension of the cervix and uterus during labor. Additionally oxytocin also assists in birth, maternal connection and after stimulation of the nipples lactation (Grasa *et al*., 2004). Medicinal plants are also recognized for their oxytocic potential. Through stimulating oxytocin receptor oxytocin increases uterine contractility. The receptor is interlinked to GPCR which supplementary activates phospholipase C. Furthermore it is followed by endorsement of Ca discharge from SR that results in myometrial tightening (Ratz *et al*., 2005). Thus our study clearly revealed that *A. foliosa n*-hexane leaves extract disturbed the Ca concentration and calibration from SR by means of G-protein signaling corridor. Thus, it may be concluded that *A. foliosa* (*n*-hexane leaves extract) may possibly operate like the blocker of oxytocin receptor *in vivo*. Oxytocin-induced contraction in the existence of elevated K solution is not only introduced by Ca-dependent corridor, additionally it might also involve to a minor degree Ca-independent pathways by way of stimulation of Rho-associated Kinase (ROK) flow. ROK mediated MLCP effect may be due to the influence of oxytocic action (World Health Organization, 2013). In our studies, the *A. foliosa n*-hexane leaves extract caused momentous decline in force through oxytocin-induced contraction due to elevated K level. Thus showing the inhibitory action of *n*-hexane leaves extract in blocking the ROK pathways.

The oxytocic screening of *Androsace foliosa (n*-hexane leaves extract) established agonistic action which are equivalent in extent with oxytocin. This experiential uterus-contracting activity of *n*-hexane leaves extract of *Androsace foliosa* was rapid in onset. The uterus-contracting action of this plant extract would be exclusively removed by washing with the extract free De-Jalon's solution. This might propose the existence of small molecular weight active chemical constituents (s) in the extract, which infiltrated rapidly to its location of action. *Androsace foliosa* (*n*-hexane leaves extract) show a physically powerful and progressive elevation in contraction at preliminary small level to amplify the concentration >3mg/ml which illustrates a stepwise decline in contraction. While the contraction due to oxytocin nevertheless physically powerful at low concentration of <0.1i.u/ml was stronger after 0.1 i.u /ml. Furthermore, with progressive rise in magnitude to 1.0i.u / ml after which elevation in concentration did not generate supplementary rise in magnitude.

Numerous studies revealed the survival of plentiful cholinergic receptors in the uterine smooth muscles. Stimulation of myometrial muscrinic receptors by agonists e.g. acetylcholine generate tightening of uterus (Uguru *et al*., 1998). Oxytocin is most powerful endogenous oxytocic agent. Oxytocin functions on myometrial oxytocin receptors (OT1a) straight forwardly create uterine contraction. Furthermore, it also acts on endometrial oxytocin receptors (OT1b) (Varol *et al*., 1989). Oxytocin increases prostaglandins and cholinergic discharge ensuing in uterine tightening. Phospholipase C-mediated recruitment of principally sarcoplasmic intracellular calcium all the way through inositol triphosphate is the principal intracellular mechanism. Additionally agonists begin indication transduction by binding to G protein- joined receptors in the cell membrane (Lanzafame *et al*., 2003). Atropine is muscrinic receptor antagonist relaxes smooth muscles. Atropine reduces the contractile affect of acetylcholine in the uterus (Lanzafame *et al.,* 2003). Salbutamol is accepted as β2-receptor agonists motivating mediator and it is described to generate evident decrease in uterine contractility still in dysmenorrheal women. Salbutamol as β2-agonsits is also utilized as a drug in obstetrics. Salbutamol (IV) can be used as a tocolytic agent to slow down the uterine smooth muscle to delay early labor (*Willets et al*., 2008). Accordingly pre-treatment of uterine strips with atropine (2mg/ml) and salbutamol (2µg/ml) antagonize the concentration vulnerably to maximum reaction to the plant extract (0.01-10 mg/ml). Furthermore, receptors resulting in a uterotonic action by a mode of action possibly by means of the prostaglandins

and motivation of adrenergic, cholinergic and oxytocic receptors.

CONCLUSION

The current study revealed that *A. foliosa n-* hexane leaves extract indicates dominant tocolytic effect on rabbit myometrium. The extract may probably restrain impulsive oxytocin-induced and KCl induced contraction. The *Af. n*-hexane leaves extract possibly slows down force when simply intracellular Ca supplies (sarcoplasmic reticulum) were existing. Accordingly, this extract is a potent uterine relaxant performing by numerous mechanisms. Mechanisms comprise inhibition of Ca entrance and obstruction of calibration from the internal store. *Androsace foliosa n*-hexane leaves extract phytochemical screening confirms the presence of saponins, flavonoids and alkaloids. Further studies are needed to clearly elucidate the exact mode of action of this medicinal plant as abortifacient. Furthermore, structure elucidation must be formed for constituent/constituents to clearly use them as a therapeutic agent.

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