



## Anti-anxiety Activity of Methanolic Extracts of Different Parts of *Angelica archangelica* Linn.

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### Abstract

*Angelica archangelica* Linn. is a herb distributed in tropical and subtropical regions of the world. In Indian and Chinese system of medicine, it is used for nervous disorders and cerebral diseases. Previously the aqueous extract of the *A. archangelica* was evaluated for anxiolytic activity and was found to have significant potential for the same. The present study is aimed to evaluate the anxiolytic activity of methanol extract of root (MER), stem (MES), leaf (MEL), fruit (MEF) and whole plant (MEW) of *Angelica archangelica* Linn. All the extracts (MER, MES, MEL, MEF and MEW) were evaluated for anxiolytic effects using elevated plus maze test (EPM) model in rats. Methanol extracts of different parts of *A. archangelica* had increased number of entries and time spent in open arms while they decreased the number of entries and duration of time spent in closed arm of the EPM. In a similar fashion, the diazepam increased the percentage of time spent and percentage of arm entries in the open arms (\* $P < 0.05$ , \*\* $P < 0.01$ ). Whole plant and the root had the maximum, leaf and fruits showed intermediate, while stem had the least anxiolytic activity (\* $P < 0.05$ , \*\* $P < 0.01$ ) in EPM (Figure 1-5). The head dip count in DZ, SMR400, SML400, SMF400 and SMW400 in open arm are significantly shown in Table 1. The DZ, SMF400 and SMW did not show the fecal bolus while other groups were reduced the fecal bolus significantly (\*\* $P < 0.01$ ) as compared to control (Table 1). Whole plant and leaf showed the most, root and fruit the intermediate and stem the least anxiolytic activity (\*\* $P < 0.01$ ) in EPM.

**Key words:** *Angelica archangelica*; Anxiolytic; Elevated plus maze test

### Introduction

According to the World Health report, approximately 450 million people suffer from serious brain/mental or behavioral disorder, yet only a few of them receive even the most basic treatment. In the search for new therapeutic agents for the treatment of neurological disorders, medicinal plant research, worldwide, has progressed constantly, demonstrating the pharmacological effectiveness of different plant species in a variety of animal models (Zhang, 2004). For centuries, plant and plant products have been used for treating various illnesses. Today, several medicinal plants and their products are still being employed as

house remedies, over the counter drugs as well as raw materials for the pharmaceutical industry and they represent a substantial proportion of the global drug market.

*A. archangelica* (Fam. Apiaceae) commonly known as Canda is a tall perennial herb with thick hollow stem bearing large bipinnate leaves and umbels of greenish-white flowers; found wild in inner valleys of Himalayas viz. Kashmir, Chamba, Kullu, Pangi, Lahaul and Kinnaur at altitudes between 3200 and 4200 m. (India). *A. archangelica* has been long and widely used in folk medicine and it is one of the most respected medicinal herbs in Nordic countries, where

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it was cultivated during the Middle Ages and exported to other parts of Europe (Sigurdsson et al, 2004). *A. archangelica* is believed to possess angelic healing power. This plant has been used in traditional and folk medicine as remedy for nervous headaches, anxiety, fever, skin rashes, wounds, rheumatism, and toothaches (Bhat et al., 2011). In Chinese system of medicine it is used for cerebral diseases (Howes et al., 2003; Rose, 2001). Phytochemical investigations on *A. archangelica* have revealed the presence of various types of secondary metabolites, predominantly furanocoumarins and volatile oils. It also contains selimone, archangelin, and oxypeucedanin, Glycoside[(3'R)-hydroxymarmesin 4'-O-β -D-lucopyranoside]. The most abundant furanocoumarins in the tincture of the fruits are imperatorin, xanthotoxin, isoimperatorin, oxypeucedanin, psoralen and bergapten. (Bhat et al., 2011)

## Materials and methods

### Plant material

The plant specimen of *Angelica archangelica* Linn. was collected from the forest of Gulmarg Hills of Jammu and Kashmir, India. The plant was identified and authenticated by Dr. Zulfiqar Ali Bhat, from Department of Pharmaceutical Sciences, University of Kashmir, Srinagar-190006, India (Voucher specimen number - KUAA01).

### Drying and size reduction of plant

The root, stem, leaf, fruit and whole plant material of *A. archangelica* were subjected to shade drying for about 1 week. The dried plant material was further crushed to powder and the powder was passed through sieve mesh 40 and stored in air tight container for further analysis.

### Extraction of plant material

The coarsely powdered material of root, stem, leaf, fruit and whole plant (1 kg each) were subjected to extraction in a soxhlet apparatus with methanol (95%) to yield 12.8%, 7.3%, 9.8% 6.4% and 13.4% w/w respectively. MER, MES, MEL, MEF and MEW were concentrated and dried on water bath to get respective extracts.

### Animals

Albino rats (Wistar Strain) of either sex weighing 150-200 gram respectively were used for studies. The albino rats were obtained from animal house of Indian

Institute of Integrative Medicine - Jammu, Jammu and Kashmir, India. They were housed in polypropylene cages with standard pellet chow and water ad libitum. In all other experimental sets, six rats were used for each dosage. Control group received only vehicle and positive control received standard drug Diazepam (1 mg/kg po) while other groups received the extracts. This Institution is approved by Committee for the purpose of control and supervision of experiments on animals (CPCSEA), Government of India. (Approval No.801/03/ca/CPCSEA).for carrying out animal studies and the protocol for the present study was approved by Institutional Animal Ethical Committee [Approval no. F-IAEC (Pharm. Sc.) APPROVAL/2011/01] and the experiments were conducted as per approved protocol.

**Acute Toxicity Study** (Organization for Economic Cooperation and Development (OECD) Guidelines-425, 2001)

Acute toxicity study was conducted as per the internationally accepted protocol drawn under the OECD guidelines 425 (OECD, 2001). Overnight fasted, healthy rats (n = 6) were administered orally the methanolic extract of root, stem, leaf, fruits and whole plant material in the doses of 1600 and 3200 mg/kg body weight and observed continuously for 4 h and after 24 h for any abnormality and mortality. All extracts at a dose level of 3200 mg/kg were found safe. Doses of 200 and 400 mg/kg were selected as experimental dose of extracts for anti-anxiety studies.

### Drugs

Diazepam (DZ) was obtained from Ranbaxy Laboratories Limited, Himachal Pradesh State Industrial Development Corporation (HPSIDC) -Baddi, Solan (India). Sodium carboxymethyl cellulose was purchased from Central drug house (p) Ltd, Post Box. No. 7138, New Delhi-110002 (India). Diazepam and Methanolic extract of root, stem, leaf, flower and whole plant of *A. archangelica* were suspended in a 1% sodium carboxymethyl cellulose solution. All the drugs were prepared immediately before use and administered orally. Control rats received 1% aqueous sodium carboxymethyl cellulose solution only. The effects of the drugs were estimated 60 minutes after drug administration. Tests were performed only after the rats had been acclimatized to the experimental environment for at least 7 days. All experiments were carried out between 09:00 and 16:00 h. In each experiment, apparatus was cleaned using 5% ethanol before introducing the next animal to preclude the possible

cueing effects of odors left by previous subjects.

### Elevated plus-maze test

The test procedure and scoring methodology for EPM have been described in detail elsewhere (Hogg, 1996; Rodgers et al., 1997). In brief, the apparatus composed of two open arms (50 x 10 cm) and two enclosed arms of the same size with 40 cm high wall arranged so that the arms of the same type were opposite to each other with a central square of 10 cm to form a plus sign. The apparatus was wooden and was elevated to a height of 50 cm above floor level by a single central support. A slight raised edge on the open arms (0.25 cm) provided additional grip for the animals, whereas open arm activity was further encouraged by testing under in a dimly lit room. The experiment was conducted between 9 –16:00 hr. To facilitate adaptation to new surroundings, rats were transported to the laboratory at least 1 h prior to testing. The trial was started by placing an animal on the central platform of the maze facing an open arm. Standard 5-min test duration was used and between subjects, the maze was thoroughly cleaned. Rats were randomly allocated to the following groups: vehicle control, positive control: Diazepam (DZ; 1 mg/kg po), MER, MES, MEL, MEF and MEW (200 and 400 mg/kg po). The animal was placed at the central platform of the maze facing an open arm. Standard 5-min test duration was used and between subjects, the maze was thoroughly cleaned. The experiments were performed with an observer unaware of the treatment of the rats inside the room. The following parameters are classically measured in this test: frequency and duration (s) of arm visits, separately for open and closed arms. A mouse was considered to have entered an arm when all four paws were on the arm. The percentage of entries into open arms, closed arms (open or closed arm entries/total arm entries $\times$ 100; % open or closed arm entries) and the percentage of time spent in open or closed arms (open or closed arm time/total arm time $\times$ 100; % open or closed arm time) are used as traditional indices of the anxiety. The latency time was also recorded i.e time spent at the center of the maze. In addition, the head dip count, raring, foci bolus (stool bal) and latency time was also recorded i.e time spent at the center of the maze (Kumar et al., 2012; Rodgers and Johnson, 1995).

### Statistical Analysis

All observations were presented as Mean  $\pm$  SEM and were analyzed using one-way analysis of variance

(ANOVA) followed by Dunnett's ( $*P < 0.05$ ,  $**P < 0.01$ ). P values lower than 0.05 were considered statistically significant.

### Results

#### Effect of DZ, MER, MES, MEL, MEF and MEW on EPM of rats

In order to determine the anxiolytic effect of DZ (1mg/kg) and MER, MES, MEL, MEF and MEW (200 and 400 mg/kg, po) of root, stem, leaf, fruit and whole plant of *A. archangelica* on the EPM, All extracts of *A. archangelica* at a dose of 400 mg/kg significantly increased the percentage of time spent and entries in the open arms while decreased the numbers of entries and duration of time spent in closed arm. In a similar fashion, the standard drug, diazepam, increased the percentage of time spent and entries in the open arms ( $*P < 0.05$ ,  $**P < 0.01$ ). Whole plant and root have shown the most, fruit and leaf intermediate and stem had the least anxiolytic activity ( $*P < 0.05$ ,  $**P < 0.01$ ) in EPM (Figure 1-5). The head dip count in DZ, SMR400, SML400, SMF400 and SMW400 in open arm are significantly shown in Table 1. The DZ, SMF400 and SMW did not show the fecal bolus while other groups were reduced the fecal bolus significantly ( $**P < 0.01$ ) as compared to control (Table 1). Whole plant and leaf showed the most, root and fruit the intermediate and stem the least anxiolytic activity ( $**P < 0.01$ ) in EPM (Figure 1-5; Table 1).

### Discussion

Evaluation of the effects of medicinal plants on organs and systems has contributed to the development of the scientific basis for their therapeutic application and also has enriched considerably the therapeutic arsenal for the treatment of a number of diseases (Kumar et al., 2011c). A number of phytoconstituents like Linalool, hypericin, cardiospermin, chrysin, cinnamic acid, p-coumaric acid, caffeic acid, ferulic acid, sinapic acid, sanjoinine A, obovatol, magnolol, honokiol, quercetin and kaempferol, apigenin etc. isolated from plants have shown promising anxiolytic activity (Kumar et al., 2011a). Previously the phytochemical screening of *A. archangelica* Linn. showed the presence of coumarins, phenolics, tannins, flavonoids, glycosides, saponins, alkaloids, carbohydrates, steroids, terpenoids etc. (Kumar et al., 2011b) and these are the compounds of interest in future for isolation which may have the

potential for anxiety.

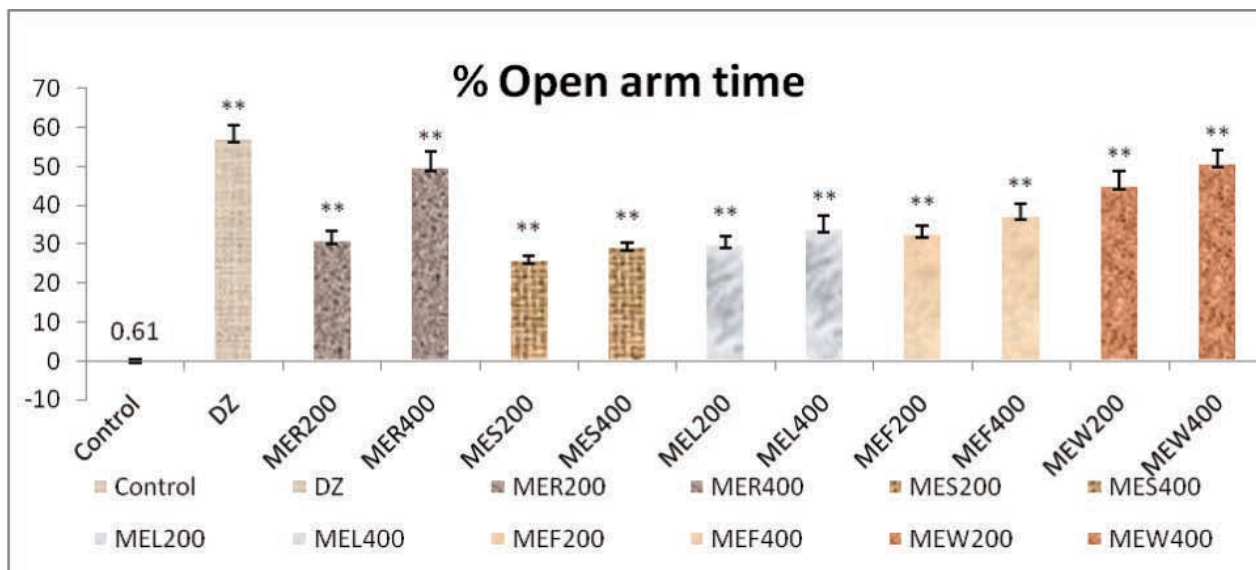
The Elevated Plus-maze is a well-established animal model and is currently the first choice test for anxiolytic drugs and has been validated for both rats and mice. It is based on the natural conflict between the drive to explore a new environment and the tendency to avoid potentially dangerous area. More recently, it has been argued that the incorporation of a range of ethological parameters may enhance the utility of this paradigm (Kumar et al., 2012). In the present study we used the EPM model of anxiety to evaluate the anxiolytic effects of *A. archangelica*. As expected, diazepam produced significant increase in time spent and number of entries into open arms and at the same time showing decreased number of entries and time spent in the closed arm. Using the EPM test, extracts of *A. archangelica*, markedly increased the percentage of time spent and arm entries in the open arms and decreased the percentage of time spent and arm entries in the closed arm. The decreased aversion to the open arms is a result of an anxiolytic effect expressed by an increased number of open arm entries and time spent in the EPM. Therefore, the behavioral alterations induced by the extracts in the EPM are consistent with an anxiolytic effect, similar to that of diazepam. In the this study, we found that whole plant and root have shown the most, fruit and leaf intermediate and stem had the least anxiolytic activity (\* $P < 0.05$ , \*\* $P < 0.01$ ) in EPM. The results clearly guided us that the whole plant and roots are the first choice of interest for further studies although all the extracts have the anxiolytic potential. Further investigations are required to identify the active constituents of the *A. archangelica* responsible for the anxiolytic effects. The results obtained from this study support the use of this important medicinal plant in the Indian and Chinese traditional medicine for the management of nervous and cerebral disorders including anxiety. Further studies are in progress in our laboratory to isolate and identify the components responsible for anxiolytic activity and the mechanism of action involved. Results will pave a way for the isolation of bioactive principles and new drug search for anxiety.

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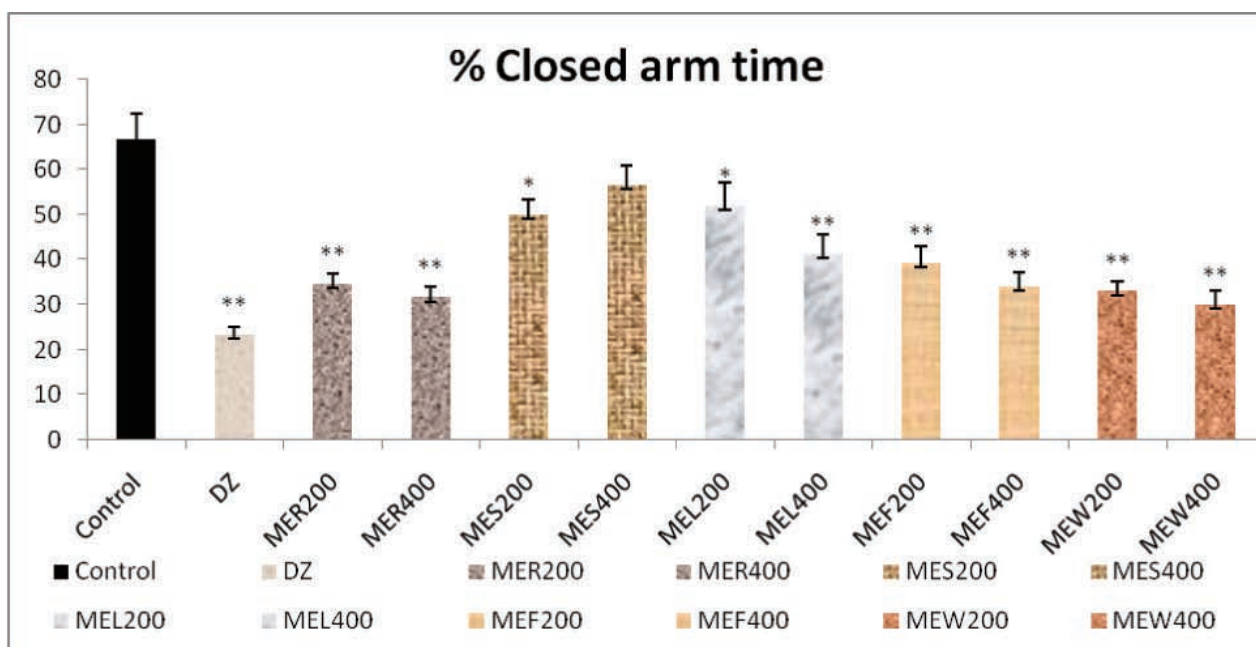
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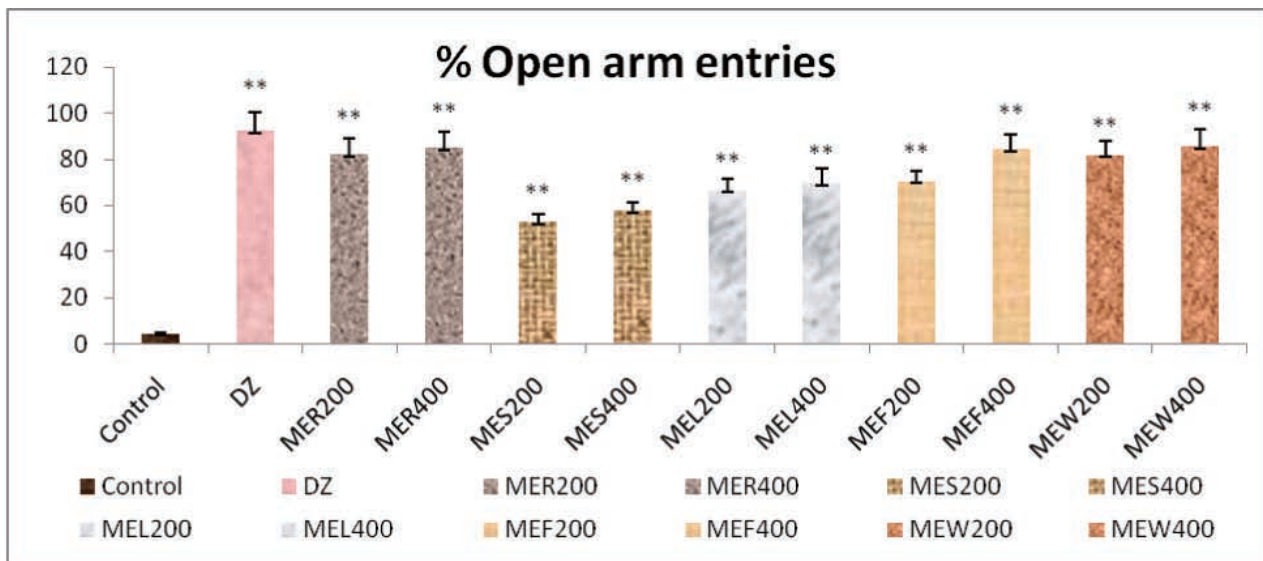
**Figure 1:** Percentage of time spent in open arm of the EPM

Results are expressed as means  $\pm$  S.E.M. (n=6). Control = vehicle, DZ = Diazepam (1mg/kg po) as a standard drug, MER 200 = Methanol extract of root of *A. archangelica* Linn. (200 mg/kg po), MER 400 = Methanol extract of root of *A. archangelica* Linn. (400 mg/kg po), MES 200 = Methanol extract of stem of *A. archangelica* Linn. (200 mg/kg po), MES 400 = Methanol extract of stem of *A. archangelica* Linn. (400 mg/kg po), MEL 200 = Methanol extract of leaf of *A. archangelica* Linn. (200 mg/kg po), MEL 400 = Methanol extract of leaf of *A. archangelica* Linn. (400 mg/kg po), MEF 200 = Methanol extract of fruit of *A. archangelica* Linn. (200 mg/kg po), MEF 400 = Methanol extract of fruit of *A. archangelica* Linn. (400 mg/kg po), MEW 200 = Methanol extract of whole plant of *A. archangelica* Linn. (200 mg/kg po), MEW 400 = Methanol extract of whole plant of *A. archangelica* Linn. (400 mg/kg po), \* $P < 0.05$ , \*\* $P < 0.01$ , all groups compared with vehicle (control). Statistically analysed by ANOVA followed by Dunnet's test.



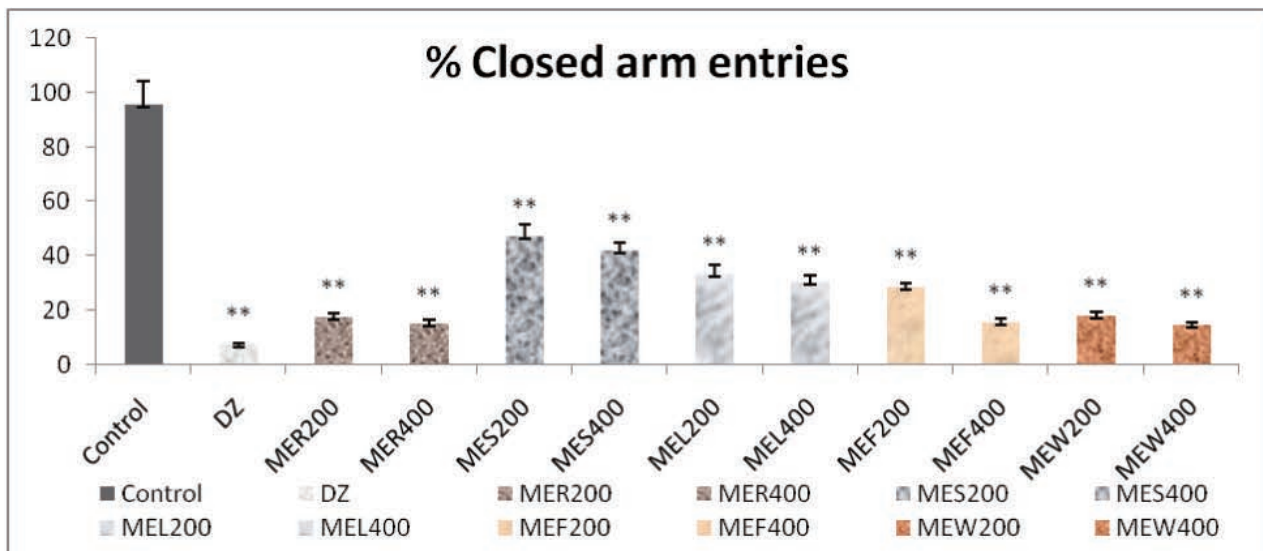
**Figure 2:** Percentage of time spent in closed arm of the EPM

Results are expressed as means  $\pm$  S.E.M. (n=6). Control = vehicle, DZ = Diazepam (1mg/kg po) as a standard drug, MER 200 = Methanol extract of root of *A. archangelica* Linn. (200 mg/kg po), MER 400 = Methanol extract of root of *A. archangelica* Linn. (400 mg/kg po), MES 200 = Methanol extract of stem of *A. archangelica* Linn. (200 mg/kg po), MES 400 = Methanol extract of stem of *A. archangelica* Linn. (400 mg/kg po), MEL 200 = Methanol extract of leaf of *A. archangelica* Linn. (200 mg/kg po), MEL 400 = Methanol extract of leaf of *A. archangelica* Linn. (400 mg/kg po), MEF 200 = Methanol extract of fruit of *A. archangelica* Linn. (200 mg/kg po), MEF 400 = Methanol extract of fruit of *A. archangelica* Linn. (400 mg/kg po), MEW 200 = Methanol extract of whole plant of *A. archangelica* Linn. (200 mg/kg po), MEW 400 = Methanol extract of whole plant of *A. archangelica* Linn. (400 mg/kg po), \* $P < 0.05$ , \*\* $P < 0.01$ , all groups compared with vehicle (control). Statistically analysed by ANOVA followed by Dunnet's test.



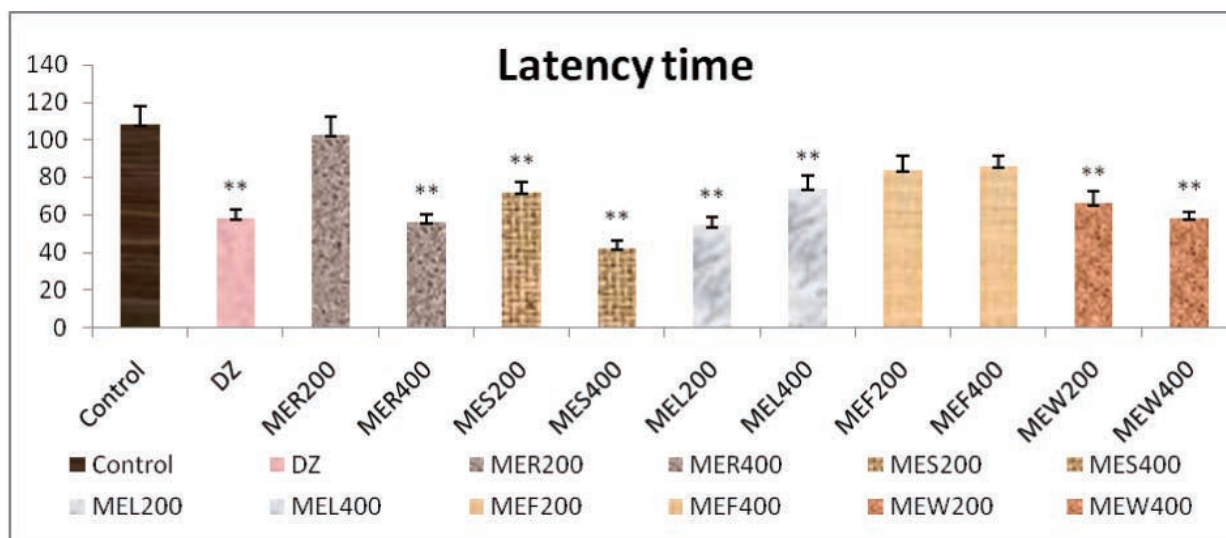
**Figure 3:** Percentage of entries in open arm of the EPM

Results are expressed as means  $\pm$  S.E.M. (n=6). Control = vehicle, DZ = Diazepam (1mg/kg po) as a standard drug, MER 200 = Methanol extract of root of *A. archangelica* Linn. (200 mg/kg po), MER 400 = Methanol extract of root of *A. archangelica* Linn. (400 mg/kg po), MES 200 = Methanol extract of stem of *A. archangelica* Linn. (200 mg/kg po), MES 400 = Methanol extract of stem of *A. archangelica* Linn. (400 mg/kg po), MEL 200 = Methanol extract of leaf of *A. archangelica* Linn. (200 mg/kg po), MEL 400 = Methanol extract of leaf of *A. archangelica* Linn. (400 mg/kg po), MEF 200 = Methanol extract of fruit of *A. archangelica* Linn. (200 mg/kg po), MEF 400 = Methanol extract of fruit of *A. archangelica* Linn. (400 mg/kg po), MEW 200 = Methanol extract of whole plant of *A. archangelica* Linn. (200 mg/kg po), MEW 400 = Methanol extract of whole plant of *A. archangelica* Linn. (400 mg/kg po), \* $P < 0.05$ , \*\* $P < 0.01$ , all groups compared with vehicle (control). Statistically analysed by ANOVA followed by Dunnet's test.



**Figure 4:** Percentage of entries in closed arm of the EPM

Results are expressed as means  $\pm$  S.E.M. (n=6). Control = vehicle, DZ = Diazepam (1mg/kg po) as a standard drug, MER 200 = Methanol extract of root of *A. archangelica* Linn. (200 mg/kg po), MER 400 = Methanol extract of root of *A. archangelica* Linn. (400 mg/kg po), MES 200 = Methanol extract of stem of *A. archangelica* Linn. (200 mg/kg po), MES 400 = Methanol extract of stem of *A. archangelica* Linn. (400 mg/kg po), MEL 200 = Methanol extract of leaf of *A. archangelica* Linn. (200 mg/kg po), MEL 400 = Methanol extract of leaf of *A. archangelica* Linn. (400 mg/kg po), MEF 200 = Methanol extract of fruit of *A. archangelica* Linn. (200 mg/kg po), MEF 400 = Methanol extract of fruit of *A. archangelica* Linn. (400 mg/kg po), MEW 200 = Methanol extract of whole plant of *A. archangelica* Linn. (200 mg/kg po), MEW 400 = Methanol extract of whole plant of *A. archangelica* Linn. (400 mg/kg po), \* $P < 0.05$ , \*\* $P < 0.01$ , all groups compared with vehicle (control). Statistically analysed by ANOVA followed by Dunnet's test.



**Figure 5:** Latency time in the EPM

Results are expressed as means ± S.E.M. (n=6). Control = vehicle, DZ = Diazepam (1mg/kg po) as a standard drug, MER 200 = Methanol extract of root of *A. archangelica* Linn. (200 mg/kg po), MER 400 = Methanol extract of root of *A. archangelica* Linn. (400 mg/kg po), MES 200 = Methanol extract of stem of *A. archangelica* Linn. (200 mg/kg po), MES 400 = Methanol extract of stem of *A. archangelica* Linn. (400 mg/kg po), MEL 200 = Methanol extract of leaf of *A. archangelica* Linn. (200 mg/kg po), MEL 400 = Methanol extract of leaf of *A. archangelica* Linn. (400 mg/kg po), MEF 200 = Methanol extract of fruit of *A. archangelica* Linn. (200 mg/kg po), MEF 400 = Methanol extract of fruit of *A. archangelica* Linn. (400 mg/kg po), MEW 200 = Methanol extract of whole plant of *A. archangelica* Linn. (200 mg/kg po), MEW 400 = Methanol extract of whole plant of *A. archangelica* Linn. (400 mg/kg po), \**P* <0.05, \*\**P* <0.01, all groups compared with vehicle (control). Statistically analysed by ANOVA followed by Dunnet's test.

**Table 1:** Effect of methanol extract of different parts of *A. archangelica* Linn.on allied parameters of EPM test

Groups	Control	DZ Cont	SMR200	SMR400	SMS200	SMS400	SML200	SML400	SMF200	SMF400	SMW200	SMW400
			S00	S00	S200	S400	ML20	400	ML20	200		
L	99.1 ± 7.01	45.3 ± 4.21**	59.5 ± 5.1**	44 ± 3.11**	50.5 ± 4.11**	44.5 ± 3.9**	54.4 ± 3.66**	44.3 ± 4.06**	54.3 ± 3.91**	43.2 ± 2.99**	58.4 ± 5.11**	40.3 ± 4.03**
HD	1.0 ± 0.10	4.0 ± 0.26**	1.0 ± 0.09	2.0 ± 0.17**	1.0 ± 0.11	1.0 ± 0.12	1.0 ± 0.1	3.0 ± 0.21**	1.0 ± 0.1	2.0 ± 0.09**	1.0 ± 0.06	3.0 ± 0.09**
FB	6.0 ± 0.56	-	2.0 ± 0.12**	1.0 ± 0.09**	3.0 ± 0.23**	2.0 ± 0.19**	1.0 ± 0.11**	1.0 ± 0.1**	2.0 ± 0.04**	-	1.0 ± 0.09**	-
CAR	7.4 ± 0.66	0.7 ± 0.04**	1.1 ± 0.10**	1.2 ± 0.11**	3.4 ± 0.36**	2.5 ± 0.21**	2.1 ± 0.2**	0.9 ± 0.09**	-	1.1 ± 0.09**	1.5 ± 0.15**	0.8 ± 0.08**

L = Latency (Time spent at the center of maze), HD = Head dip count (Head dip from the open arm), FB = Fecal bolus (stool balls), CAR = Closed arm returns, Results are expressed as means ± S.E.M. (n=6). Control = vehicle, DZ = Diazepam (1mg/kg po) as a standard drug, MER 200 = Methanol extract of root of *A. archangelica* Linn. (200 mg/kg po), MER 400 = Methanol extract of root of *A. archangelica* Linn. (400 mg/kg po), MES 200 = Methanol extract of stem of *A. archangelica* Linn. (200 mg/kg po), MES 400 = Methanol extract of stem of *A. archangelica* Linn. (400 mg/kg po), MEL 200 = Methanol extract of leaf of *A. archangelica* Linn. (200 mg/kg po), MEL 400 = Methanol extract of leaf of *A. archangelica* Linn. (400 mg/kg po), MEF 200 = Methanol extract of fruit of *A. archangelica* Linn. (200 mg/kg po), MEF 400 = Methanol extract of fruit of *A. archangelica* Linn. (400 mg/kg po), MEW 200 = Methanol extract of whole plant of *A. archangelica* Linn. (200 mg/kg po), MEW 400 = Methanol extract of whole plant of *A. archangelica* Linn. (400 mg/kg po), \**P* <0.05, \*\**P* <0.01, all groups compared with vehicle (control). Statistically analysed by ANOVA followed by Dunnet's test.