Phytochemical screening and antipyretic effects of hydroalcoholic extracts of selected medicinal plants of Rawalakot, Azad Jammu and Kashmir in albino rats

Mahvish Ajaz[1], Muhammad Akram[1, 4], Hafiz Muhammad Asif[2], Abid Hussain[3], Syed Muhammad Ali Shah[4], Imtiaz Mahmood Tahir[5], Muhammad Daniyal*[6] and Fahad Said Khan[1]

[1]Department of Eastern Medicine, Faculty of Medical and Health Sciences, The University of Poonch, Rawalakot, Azad Jammu and Kashmir, Pakistan
[2]Department of Eastern Medicine, University College of Conventional Medicine, Faculty of Pharmacy and Alternative Medicine, The Islamia University of Bahawalpur, Bahawalpur, Pakistan
[3]Department of Pharmacy, Faculty of Medical and Health Sciences, The University of Poonch, Rawalakot, Azad Jammu and Kashmir, Pakistan
[4]Department of Eastern Medicine, Directorate of Medical Sciences, Government College University, Faisalabad, Pakistan
[5]College of Allied Health Professionals, Directorate of Medical Sciences, Government College University, Faisalabad, Pakistan
[6]TCM and Ethnomedicine Innovation & Development Laboratory, School of Pharmacy, Hunan University of Chinese Medicine, Changsha, China

Abstract: Pyrexia occurs due to infection, malignancy and other diseases. Majority of the antipyretic drugs are synthetic in nature which exerts side effects such as gastric ulcer, hepatic necrosis and renal damage. The antipyretic potential of the hydro-alcoholic extracts of *Achillea millefolium, Taraxacum officinale, Salix alba* and *Trigonella foenum* were investigated on the yeast-induced pyrexia in albino rats. Paracetamol was used as a positive control. Rectal temperature of albino rats was verified immediately before the administration of the extracts or vehicle or paracetamol and yet again at 1-hour gap for 6 hours using a digital thermometer. The animals having pyrexia were divided into four groups Group1: Paracetamol was given to positive control. Group 2: Distilled water was given to negative control. Group 3: (250mg/kg) extract of the plant was given to rats (treatment group 1). Group 4: (500mg/kg) extracts of the plant was given to albino rats (Treatment group 2). The extracts were also phytochemically screened for alkaloids, tannins, saponins, flavonoids, cardiac glycosides and phenols. The hydro-alcoholic extracts of plants with the dose of 500mg/kg showed significant ($p<0.0001$) decrease in yeast-induced pyrexia, as compared with that of set drug paracetamol (150mg/kg) where the extract dose 250mg/kg was less effective than that of standard drug ($p<0.05$). Phytochemical screening showed the presence of alkaloids, tannins, flavonoids, saponins and phenols. This study showed that hydro-alcoholic extracts of all plants under study at a dose of 500mg/kg have significant antipyretic potential in yeast-induced elevated temperature.

Keywords: Acetaminophen, antipyretic drugs, fever, paracetamol, plant extract, yeast-induced pyrexia.

INTRODUCTION

Pyrexia is a frequent medical symptom that is described as increasing in internal body temperature to a level above the normal, characterized by temperature elevation in body's thermoregulatory set and it occurs when there is a disorder in hypothalamic set point. Fever is produced by the generation of pyrogens which provoke prostaglandin E2. Prostaglandins proceed on the hypothalamus, which produces areaction on the entire body and results in a new temperature level (Kozak *et al.,* 2000). Increase in body temperature is the response given by human body due to inflammation, tissue damage, cancer and this term is labeled as pyrexia or more commonly fever (Rajani *et al*., 2011). The branch of Ayurveda best describes the beginning of fever as the combination of indigestion, seasonal changes and alternation of the daily routine. Children in developing World are exposed to malnutrition and unsafe hygiene practices which in turn the body responds to it in the form of fever. This fever also connects with body pain and aches which is the fundamental cause of the increase in the disease and death count (Ighodaro *et al.,* 2009). Nowadays research in pain management has enabled us to use natural products in their original form. Treatment of pain with medicinal plants lessens the risk of addiction. The aim of the study is to find out the antipyretic activity of medicinal plants in albino rats against yeast induced pyrexia. Secondly to compare the antipyretic action of plants extracts with standard antipyretic agent paracetamol. Third to investigate the phytochemical analysis of plants

*Corresponding author: e-mail: daniyaldani151@yahoo.com

MATERIALS AND METHODS

Plants material

Medicinal plants (*Achillea millefolium, Taraxacum officinale, Salix alba* and *Trigonella foenum*) were

collected from Rawalakot Azad Jummu and Kashmir and were confirmed by authentication source from Department of Botany, The University of Poonch, Rawalakot, Azad Jummu and Kashmir. Voucher specimens for each plant were also deposited.

Plant extraction

The fresh green leaves of *Achillea millefolium* and *Taraxacum officinale,* the bark of *Salix alba* and seeds of *Trigonella foenum* were separated and cleaned and washed with distilled water and dried under shade at a temperature between 21-30PC for 30 days. The powdered material (500g) of *Achillea millefolium,* Taraxacum *officinale, Salix alba* and *Trigonella foenum* was taken in a beaker having a capacity of 2 litters, alcohol 70% + distilled water 30% was further, soaked for three days with intermittent shaking and moving. The deposits were extracted three times with the same clean solvent and extract united. The soaked material of plants was filtered all the way through many layers of muslin cloth individually for crude filtration. The deposit was filtered all the way through a Whatman#1 filter paper. The filtered extracts were evaporated at 40PC, in a rotary evaporator. The filtrates were placed in seal neck plastic bottles with firm closure at (20°C) temperature.

Paracetamol hydroalcoholic preparation

Paracetamol was soaked with the quantity of 15grams powder in 150ml of solvent (ethanol 105ml + distilled water 45ml) for 10 minutes. For the avoidance of unnecessary evaporation of the solvent, the container was closely tightened with aluminum sheet. Twice a day for 10 minutes, the material was shaken forcefully. The bottle was placed in the laboratory at room temperature (20°C).

Animals and experimental design

The experimental animals used in this study were albino male and female rats weighing about 150-200g. They received standard pellet diet and water *ad* libitum. The albino rats were adjusted to handlers for 1week before the start of the experiments. The rats were sub-divided into 4 groups: Group 1: Positive control: Paracetamol was given (150mg/kg), Group 2: Negative control: Distilled water was given (150ml/kg), Group 3: Treatment group I was given plant extract (250mg/kg) Group 4: Treatment group II: was given plant extracts (500mg/kg). Fever was induced in albino rats by s/c injection of 20% weight by volume of brewer s' yeast (10ml/kg) 18hours before the start of the experiment. Group 1 and 2 served as controls while group 3 and 4 served as the treatment group. Each group consisted of 6 animals.

Induction of pyrexia in experimental animals

Fever was induced by s/c injection of 20% weight by volume of brewer s' yeast (10ml/kg) in distilled water. By inserting a digital clinical thermometer to a depth of 3-4cm into the rectum, the rectal temperature of the albino rats was recorded before and after injection of yeast. Rectal temperature was noted at a regular interval during the experiment. The temperature was measured at first, second, third, fourth, fifth and 6^{th} hours after drug administration.

Preparation of extracts for injection into rats

Fever was produced after 1-2-hour injection of brewer s' yeast. The rectal temperature of the albino rats raised 2-5of from standard body temperature of rats. The hydro-alcoholic of plant extracts was given orally to rats at the dose rate of 250mg and 500mg/kg body weight which is dissolved in 3ml distilled water.

Rectal temperature determination

A digital thermometer was used for the measurement of rectal temperature. The lubricated thermometer was inserted 3-4cm deep into the rectum for 60sec. The rise in temperature was read on the digital thermometer.

Phytochemical analysis of medicinal plants

Tests were performed for detection of proteins, carbohydrates, tannins, phenols, flavonoids, saponins, glycosides, phytosterol, steroid, terpenoids and alkaloids (table 1).

Ethical approval

This study was approved by the Departmental Ethical Committee of Medical and Health Sciences Faculty, University of Poonch, Rawalakot, Azad Kashmir.

STATISTICAL ANALYSIS

The data collected was analyzed by using the analysis of variance (ANOVA) technique and difference among treatment means was compared as revealed by Duncan's Multiple Range Test (DMRT).

RESULTS

A physiological process which is characterized by an increase in the body temperature above the normal range is called pyrexia (Muhammad *et al.,* 2012). The body temperature regulating center is present in the hypothalamus When there is a disturbance in the regulatory center of the hypothalamus, fever occurs due to rise in body temperature (Enrique and Neus, 2012).

Majority of the plants have an antipyretic activity that is evident from the study conducted by Romanovsky *et al.*, (2005). The brain is responsible to tune a complex event that is known as pyrexia throughout a chain of inflammatory regulation (Inoue *et al*., 2008). The pre-optic area of the anterior hypothalamus, the final fever mediator in the brain, is prostaglandin E2 (PGE2). According to the classical view, the inflammatory mediators are responsible to induce the genesis of fever that is primarily released by activated peripheral mononuclear phagocytes and other immune cells (Roth *et al.,* 2006). Paracetamol is considered as a standard

Table1: Phytochemical analysis of plants

No.	Tests	Reagent	Color appearance	Result
1.	Tests for protein (Ninhydrine test)	Extract + 0.25% w/v ninhydrine reagent	Blue color appears	Amino acid present
2	Test for carbohydrates (Fehling's test)	Extract + 2 ml Fehling solution A, B	Brick red precipitates form	Reducing sugar
3.	Benedict's test	Extract + 2 ml of Benedict's reagent	Orange, red precipitates appear	Carbohydrates present
4.	Molisch's test	Extract + 2 ml Molisch reagent + H_2SO4	Violet ring appears	Carbohydrates present
5.	Iodine test	Extract + 2 ml iodine	Blue color appears	Starch present
6.	Test for Tannins	Extract + 1% gelatin solution containing NaCl	White color appears	Tannins present
7.	Test for Phenols	Extract + 2 ml $FeCl_3$	Bluish black color	Phenols present
8	Test for flavonoids (Test for Lead acetate)	Extract + only some drops of Pb (CH3COO)2 solution	Yellow color appears	Flavonoids present
9	Alkaline reagent test	Extract + 2 ml NaOH	Yellow color appears	Flavonoids present
10	Test for Saponins (Foam test)	Extract + 2 ml H_2O	Foams appear	Saponins present
11.	Test for glycosides (Liebermann's test)	Extract + chloroform + Acetic acid + H_2SO_4	Violet, blue, green color appears	Glycosides present
12.	Test for Phytosterol (Salkowski's test)	Extract + chloroform + H_2SO_4	Golden yellow color appears	Phytosterol (Triterpenes)
13.	Test for steroid	Extract + chloroform + H_2SO_4	Red color appears	Steroids present
13.	Test for terpenoids	Extract + chloroform + H_2SO_4	Grayish color appears	Terpenoids present
14.	Test for alkaloids	Extract + HCl + Vagners and Mayers reagent	Precipitates form	Alkaloids present

Table 2: Phytochemistry of the four medicinal plants

No.	Tests	*Achillea millefolium*	*Taraxacum officinale*	*Salix alba*	*Trigonella foenum*
1.	Tests for protein (Ninhydrine test)	+ +	+ +	+ +	+
2	Test for carbohydrates (Fehling's test)	+ +	+	+	+ +
3.	Benedict's test	+	+ +	+ +	+ +
4.	Molisch's test	+	+ +	+ +	+ +
5.	Iodine test	+	+ +	+	+
6.	Test for tannins	+ +	+ +	+ +	+ +
7.	Test for phenols	+	+	+	+ +
8.	Test for flavonoids (Lead acetate test)	++	++	+ +	+ +
9.	Alkaline reagent test	+ +	+	+ +	+
10.	Test for saponins (Foam test)	+ +	+ +	+ +	+ +
11.	Test for glycosides (Liebermann's test)	+ +	+	+	+
12.	Test for phytosterol (Salkowski's test)	+ +	+ +	+	+ +
13.	Test for terpenoids	+ +	+ +	+ +	+ +
14.	Test for alkaloids	+ +	+ +	+	+ +

antipyretic and analgesic drug. In the presence of peroxides, it is a poor inhibitor of cyclooxygenase, where peroxide quality is small. Further, it does not inhibit neutrophil activation. In supra-pharmacologic doses, it inhibits NF-KB stimulation of inducible nitric oxide synthase. In the current study, pyrexia was observed after 18 hours of yeast injection. Hydro-alcoholic extracts of *Achillea millefolium*, *Trigonella foenum*, Taraxacum *officinale* and *Salix alba* were evaluated for their anti-pyretic activity. Different doses of plant extracts were given orally to pyretic rats. All of the above-mentioned extracts notably lowered the body temperature at adose range of 250 and 500mg/kg.

Phytochemical screening

The phytochemical screening of hydro-alcoholic extracts of medicinal plants *(Achillea millefolium*, Taraxacum *officinale*, *Salix alba* and *Trigonella foenum)* have shown

Table 3: Antipyretic effect of hydro-alcoholic extract of *Achillea millefolium* leaves on Brewer's yeast induced pyrexia in rats.

No. Groups	Treatment dose mg/kg	Rectal Temperature		Rectal temperature after drug administration					
		Initial	18hrs after yeast administration	1st hr	2nd hr	3rd hr	4th hr	5th hr	6th
Control	-	38.36	40.36	40.36	40.26	39.86	39.90	39.65	39.75
Paracetamol	150 mg/kg	38.38	40.30	39.88	38.95	38.85	38.40	38.13	38.18
Extract	250 mg/kg	38.55	40.0	39.9	39.6	39.3	39.2	38.8	38.13
Extract	500 mg/kg	38.58	40.16	39.53	38.80	38.55	38.51	38.38	38.00

Table 3.1: Antipyretic effect of hydro-alcoholic extract of *Achillea millefolium* leaves 500mg/kg in rats.

No. of rats	Rectal temperature		Temperature after the administration of Dose 500mg/kg					
	Initial	Temp after administration of yeast	1st hr	2nd hr	3rd hr	4th hr	5th hr	6th
R1	38.4	40.2	39.5	39.1	38.8	38.4	38.3	38.1
R2	38.8	40.0	39.9	39.4	38.3	38.5	38.4	38.0
R3	38.4	40.0	39.4	38.8	38.6	38.6	38.3	38.0
R4	39.0	40.4	39.6	38.4	38.8	38.9	38.5	38.0
R5	38.1	40.3	39.3	38.8	38.5	38.3	38.2	38.0
R6	38.8	40.1	39.5	38.3	38.3	38.4	38.6	38.0
Mean	38.58	40.16	39.53	38.80	38.55	38.51	38.38	38.00
SD	0.33	0.16	0.20	0.41	0.22	0.21	0.14	0.08
SEM	±0.13	0.06	0.08	0.16	0.09	0.08	0.06	0.03
P value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Table 3.2: Antipyretic effect of hydro-alcoholic extract of *Achillea millefolium* leaves 250mg/kg in rats.

No of rats	Rectal temperature ºC		Temperature after the administration of Dose 250 mg/kg					
	Initial	Temp after administration of yeast	1st hr	2nd hr	3rd hr	4th hr	5th hr	6th hr
R1	38.0	40.2	39.9	39.9	39.4	39.1	38.8	38.1
R2	38.6	40.1	40.0	39.8	39.5	39.1	38.9	38.2
R3	38.6	40.0	39.9	39.5	39.3	39.3	38.9	38.0
R4	38.2	40.1	39.9	39.7	39.5	39.2	38.8	38.3
R5	38.8	39.9	39.6	39.3	39.0	38.9	38.5	38.0
R6	39.1	40.2	40.1	39.9	39.6	39.8	39.1	38.1
Mean	38.55	40.0	39.9	39.6	39.3	39.2	38.8	38.13
SD	0.39	0.10	0.13	0.11	0.11	0.17	0.17	0.36
SEM	±0.16	±0.03	±0.05	±0.04	±0.04	±0.07	±0.07	±0.14
P value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

the presence of proteins, carbohydrates, tannins, phenols, saponins, flavonoids alkaloids and glycosides (table 2).

In vivo antipyretic activity assay

The animals were treated with the brewer yeast, paracetamol and the plant extracts. The rectal temperature was first taken before treatment. After treatment, the rectal temperature was measured after 1st, 2nd, 3rd, 4th, 5th and 6th hours. The rectal temperature was determined after everydrugadministration. During the experiment, the animals were given commercial rat's pellets and drinking water *ad* libitum.

Effect of Achillea millefolium on temperature in yeast induced pyretic rats

The antipyretic effect of hydro-alcoholic extract of *Achillea millefolium* leaves in rats showed that initial rectal temperature in control rats was 38.36°C, after 18 hrs of yeast administration, the temperature rose to 40.36°C, then after every hour for 1stto 6thhours the temperature was 40.36°C, 40.26°C, 39.86°C, 39.90°C, 39.65°C and 39.75°C respectively (table 3). When a dose of 150mg/kg paracetamol was administered to positive control rats, the initial rectal temperature was 38.38°C, after 18hrs of yeast administration temperature rose to

Table 4: Antipyretic effects of hydro-alcoholic extract of *Trigonella foenum seeds* on Brewer's yeast induced pyrexia in rats.

No. Groups	Treatment dose mg/kg	Rectal Temperature		Rectal temperature after drug administration					
		Initial	18 hrs after yeast administration	1st hr	2nd hr	3rd hr	4th hr	5th hr	6th
Control	-	38.36	40.36	40.36	40.26	39.86	39.90	39.65	39.75
Paracetamol	150 mg/kg	38.58	40.30	39.88	38.95	38.85	38.40	38.13	38.18
Extract	250 mg/kg	38.76	40.48	39.95	39.63	39.15	38.61	38.43	38.61
Extract	500 mg/kg	38.90	40.40	40.60	39.96	39.53	39.11	38.91	38.26

Table 4.1: Antipyretic effect of hydro-alcoholic extract of *Trigonella foenum* seeds 500mg/kg in rats.

No. of rats	Rectal temperature °C		Temperature after the administration of Dose 500 mg/kg					
	Initial	Temp after the administration of yeast	1st hr	2nd hr	3rd hr	4th hr	5th hr	6th
R1	38.3	40.0	39.5	39.1	39.1	38.9	38.5	38.2
R2	38.8	39.9	39.1	38.8	38.9	38.6	38.5	38.2
R3	39.4	40.2	39.5	38.8	39.5	38.9	39.5	38.3
R4	38.4	41.2	39.4	39.1	38.9	38.6	39.4	38.1
R5	39.1	40.4	39.3	39.5	39.0	38.8	38.7	38.2
R6	39.4	40.0	39.5	39.5	39.3	39.0	38.4	38.2
Mean	38.90	40.40	39.58	39.38	39.53	39.11	38.91	38.26
SD	0.48	0.54	0.19	0.16	0.38	0.31	0.34	0.1966
SEM	±0.19	0.22	0.07	0.06	0.15	0.13	0.14	0.0803
P value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Table 4.2: Antipyretic effect of hydro-alcoholic extract of *Trigonella foenum* seeds 250mg/kg in rats.

No. of rats	Rectal temperature		Temperature ºC after the administration of Dose 250mg/kg					
	Initial	Temp after the administration of yeast	1st hr	2nd hr	3rd hr	4th hr	5th hr	6th
R1	39.1	40.0	39.9	39.4	39.0	38.8	38.6	38.6
R2	38.4	40.9	40.2	40.3	39.4	38.7	38.8	38.6
R3	39.4	40.5	39.9	39.3	39.0	38.5	38.3	38.6
R4	38.6	40.3	39.8	39.4	39.1	38.9	38.9	38.6
R5	38.8	41.2	40.0	39.9	39.3	38.6	38.0	38.7
R6	38.3	40.0	39.9	39.5	39.1	38.2	38.0	38.6
Mean	38.76	40.48	39.95	39.63	39.15	38.61	38.43	38.61
SD	0.4227	0.4875	0.1378	0.3882	0.1643	0.2483	0.3933	0.18
SEM	±0.1726	±0.1990	0.0563	0.1585	0.0671	0.1014	0.1606	0.07
P value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

40.30°C, then after every hour for 1st to 6th hours, the temperature was 39.88°C, 38.95°C, 38.85°C, 38.40°C 38.13°C and 38.18°C respectively. Similarly, when a dose of 250mg/kg *Achillea millefolium* leaves extract was administered to pyretic rats, the initial rectal temperature was 38.55°C, 18hrs after yeast administration temperature rose to 40.40°C, then after every hour for 1st to 6th hours the temperature was 39.9°C, 39.6°C, 39.3°C, 39.2°C, 38.8°C and 38.13°C respectively. Finally, when a dose of 500mg/kg *Achillea millefolium* leaves extract was administered to pyretic rats, the initial rectal temperature was 38.58°C, after 18hrs of yeast administration, temperature rose to 40.16°C, then after every hour for 1st to 6th hours the temperature was 39.53°C, 38.80°C, 38.55°C, 38.51°C, 38.38°C and 38.00°C respectively.

The antipyretic effect of ahydro-alcoholic extract of *Achillea millefolium* leaves in rats given in table 3.1 showed that average initial rectal temperature of six rats was 38.58°C with SD of 0.33, SEM of ±0.13. After 18 hours of yeast administration, the average rectal temperature was 40.16°C with SD of 0.16, SEM of ±0.06. At 6th hour of extract administration (500mg/kg), the average rectal temperature was 38.00°C with SD of 0.08, SEM of ±0.03 with a very highly significant P-value of (<0.0001).

Table 5: Antipyretic effect of hydro-alcoholic extract of *Taraxacum officinale* leaves on Brewer's yeast induced pyrexia in rats.

No. Groups	Treatment dose mg/kg	Rectal Temperature		Rectal temperature after drug administration					
		Initial	18 hrs after yeast administration	1st hr	2nd hr	3rd hr	4th hr	5th hr	6th
Control	-	38.36	40.38	40.36	40.26	39.86	39.90	39.65	39.75
Paracetamol	150mg/kg	38.38	40.30	39.88	38.95	38.85	38.40	38.13	38.18
Extract	250mg/kg	38.83	40.41	39.06	39.78	39.11	39.18	38.71	38.50
Extract	500 mg/k	38.71	40.28	39.81	38.76	38.83	38.46	38.23	38.35

Table 5.1: Antipyretic effect of hydro-alcoholic extract of *Taraxacum officinale* leaves 500 mg/kg in rat.

No. of rats	Rectal temperature ºC		Temperature after the administration of Dose 500mg/kg					
	Initial Rectal temperature	Temp after the administration of yeast	1st hr	2nd hr	3rd hr	4th hr	5th hr	6th
R1	39.3	40.4	40.0	39.8	39.6	39.4	39.1	38.3
R2	38.6	40.6	39.8	39.6	39.3	38.9	38.5	38.3
R3	38.5	40.3	39.8	39.4	39.0	38.3	38.3	38.3
R4	38.7	40.3	39.5	39.2	38.9	38.4	38.5	38.5
R5	38.4	39.9	39.3	38.8	38.6	38.2	38.3	38.3
R6	38.8	40.2	40.0	39.5	39.0	38.8	38.4	38.4
Mean	38.71	40.28	39.73	39.38	39.07	38.67	38.52	38.35
SD	0.3189	0.2317	0.2805	0.3488	0.3445	0.4546	0.2994	0.3286
SEM	±0.1302	0.0946	0.1145	0.1424	0.1406	0.1856	0.1222	0.1342
P value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Table 5.2: Antipyretic effect of hydro-alcoholic extract of *Taraxacum officinale* leaves 250 mg/kg in rats.

No. of rats	Rectal temperature		Temperature after the administration of Dose 250mg/kg					
	Initial Temp ºC	Temp after the administration of yeast	1st hr	2nd hr	3rd hr	4th hr	5th hr	6th
R1	38.4	40.2	40.0	39.9	39.6	39.5	39.0	38.6
R2	38.9	41.0	40.5	39.4	39.5	39.3	38.8	38.5
R3	39.2	40.0	39.9	39.8	39.8	39.1	38.6	38.4
R4	38.8	40.2	40.0	39.7	39.4	39.0	38.3	38.5
R5	38.7	40.6	39.9	39.9	39.4	39.1	38.7	38.5
R6	39.0	40.5	40.1	40.0	39.6	39.1	38.9	38.5
Mean	38.83	40.41	40.06	39.78	39.11	39.18	38.71	38.50
SD	0.2733	0.3601	0.2251	0.2137	0.1517	0.1835	0.2483	0.2074
SEM	±0.1116	0.147	0.0919	0.0872	0.0619	0.0749	0.1014	0.0847
P value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Table 6: Antipyretic effect of hydro-alcoholic extract of *Salix alba* bark on Brewer's yeast induced pyrexia in rats.

No. Groups	Treatment dose mg/kg	Rectal Temperature		Rectal temperature after drug administration					
		Initial	18 hrs after yeast administration	1st hr	2nd hr	3rd hr	4th hr	5th hr	6th
Control	-	38.36	40.38	40.36	40.26	39.86	39.90	39.65	39.75
Paracetamol	150mg/kg	38.38	40.30	39.88	38.95	38.85	38.40	38.13	38.18
Extract	250mg/kg	38.56	40.30	40.51	40.34	39.58	39.33	39.11	39.75
Extract	500mg/kg	38.76	40.25	40.43	40.41	40.23	40.03	39.85	38.03

Table 6.1: Antipyretic effects of hydro-alcoholic extract of *Salix alba* bark 500mg/kg in rats

No of rats	Rectal temperature		Temperature after the administration of Dose 500mg/kg					
	Initial	Temp after the administration of yeast	1st hr	2nd hr	3rd hr	4th hr	5th hr	6th
R1	38.9	39.9	40.1	39.8	39.9	39.9	39.7	38.0
R2	38.9	40.2	40.2	40.6	40.5	40.3	40.1	38.0
R3	38.4	40.4	41.0	40.2	40.2	40.0	39.9	38.1
R4	38.5	40.4	40.6	40.4	40.1	40.1	39.8	38.0
R5	39.1	40.5	40.5	41.1	40.5	40.0	39.7	38.0
R6	38.8	40.1	40.2	40.4	40.2	39.9	39.9	38.2
Mean	38.76	40.25	40.43	40.41	40.23	40.03	39.85	38.03
SD	0.2658	0.2258	0.3386	0.4309	0.2338	0.1506	0.1517	0.1862
SEM	±0.1085	0.0922	0.1382	0.1759	0.0955	0.0615	0.0619	0.0760
P value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Table 6.2: Antipyretic effect of hydro-alcoholic extract of *Salix alba* bark 250 mg/kg in rats

No of rats	Rectal temperature		Temperature after the administration of Dose 250mg/kg					
	Initial	Temp after the administration of yeast	1st hr	2nd hr	3rd hr	4th hr	5th hr	6th
R1	38.1	40.0	40.4	40.3	39.9	39.4	39.2	38.7
R2	39.1	40.6	40.5	40.2	39.5	39.3	39.1	38.6
R3	39.0	40.4	40.8	40.6	39.7	39.5	39.4	38.7
R4	38.4	40.6	41.1	40.6	39.3	39.1	39.0	38.7
R5	38.7	40.5	40.4	40.2	39.5	39.0	38.8	38.8
R6	38.1	40.2	40.0	39.9	39.6	39.7	39.2	38.7
Mean	38.56	40.38	40.51	40.34	39.58	39.33	39.11	38.75
SD	0.4367	0.2401	0.3777	0.2683	0.2041	0.2582	0.2041	0.2950
SEM	±0.1783	0.0980	0.1542	0.1095	0.0833	0.1054	0.0833	0.1204
P value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Table 7.1: Antipyretic effect of Quepidol on yeast induced pyretic rats

No. Groups	Treatment dose mg/kg	Rectal Temperature		Rectal temperature after drug administration					
		Initial	18 hrs after yeast administration	1st hr	2nd hr	3rd hr	4th hr	5th hr	6th
Control	-	38.33	40.32	40.36	40.26	39.86	39.90	39.65	39.75
Paracetamol	150mg/kg	38.39	40.30	39.88	38.95	38.85	38.40	38.13	38.18
Extract	250mg/kg	38.55	40.28	39.95	39.78	39.53	39.33	38.57	38.01
Extract	500 mg/k	38.90	40.40	39.58	38.80	38.91	38.33	38.1	37.56

The antipyretic effect of a hydro-alcoholic extract of *Achillea millefolium* leaves in rats given in table 3.2 showed that average initial rectal temperature of six rats was 38.55°C with SD of 0.39, SEM of ±0.16. After 18 hours of yeast administration, the average rectal temperature was 40.0°C with SD of 0.10, SEM of ±0.03. At 6th hours of extract administration (250mg/kg), the average rectal temperature was 38.13°C with SD of 0.36,SEM of ±0.14 with a very highly significant P-value of (<0.0001).

Effect of Trigonella foenum on temperature in yeast induced pyretic rats

The antipyretic effects of hydro-alcoholic extract of *Trigonella foenum*seeds in rats given in table 4 showed that initial rectal temperature in control rats was 38.36°C, after 18hrs of yeast administration the temperature rose to 40.36°C, then after every hour for 1st to 6th hours the temperature was 40.36°C, 40.26°C, 39.86°C, 39.90°C, 39.65°C, 39.75°C respectively (table 4). When a dose of 150mg/kg paracetamol was administered to positive control rats, the initial rectal temperature was 38.58°C. After 18hrs of yeast administration, the temperature was raised to 40.16°C, then after every hour for 1st to 6th hours, the temperature was 39.88°C, 38.95°C, 38.85°C, 38.40°C, 38.13°C and 38.18°C respectively. Similarly, when a dose of 250mg/kg *Trigonella foenum* seeds extract was administered to pyretic rats, the initial rectal temperature was 38.76°C, after 18hrs of yeast administration, temperature rose to 40.48°C, then after

Table 7.2: Antipyretic effect of hydro-alcoholic extract of Quepidol 250mg/kg in rats

No. of rats	Rectal temperature °C		Temperature ºC after the administration of Dose 250mg/kg					
	Initial	Temp after the administration of yeast	1st hr	2nd hr	3rd hr	4th hr	5th hr	6th
R1	38.0	40.4	39.9	39.9	39.1	39.4	38.8	38.1
R2	38.6	40.6	40.2	39.4	38.9	39.3	38.6	38.1
R3	38.6	40.3	39.9	39.8	39.5	39.5	38.5	38.0
R4	38.2	40.3	39.8	39.7	38.9	39.1	38.4	38.4
R5	38.8	39.9	40.0	39.9	39.0	39.0	38.4	38.3
R6	39.1	40.2	39.9	40.0	39.3	39.7	38.7	38.2
Mean	38.55	40.28	39.95	39.78	39.53	39.33	38.57	38.1
SD	0.39	0.2317	0.1378	0.2137	0.38	0.2582	0.16	0.12
SEM	±0.16	0.0946	0.0563	0.0872	0.15	0.1054	0.06	0.04
P value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Table 8: Antipyretic effect of Paracetamol on brewer's yeast induced pyrexia in rats

No of rats	Rectal temperature ºC		Temperature after the administration of Dose 150mg/kg					
	Initial	Temp after the administration of yeast	1st hr	2nd hr	3rd hr	4th hr	5th hr	6th hr
R1	38.4	40.1	39.5	39.0	38.8	38.6	38.4	38.2
R2	38.1	40.2	39.7	39.1	38.6	38.5	38.3	38.1
R3	38.4	39.9	39.4	38.8	38.5	38.8	38.5	38.2
R4	38.7	40.0	39.4	38.9	38.4	38.5	38.3	38.1
R5	38.3	40.1	39.5	38.8	38.4	38.4	38.3	38.2
R6	38.4	40.0	39.5	39.0	38.7	38.4	38.2	38.1
Mean	38.38	40.05	39.50	38.93	38.57	38.53	38.33	38.15
SD	0.19	0.10	0.10	0.12	0.16	0.15	0.10	0.05
SEM	0.07	0.04	0.04	0.04	0.06	0.06	0.04	0.02
P value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Table 9: Control group receiving distilled water

No of rats	Rectal temperature		Temperature after the 18 hrs of yeast injection					
	Initial	Temp after the administration of yeast	1st hr	2nd hr	3rd hr	4th hr	5th hr	6th
R1	38.2	40.5	40.3	40.1	39.9	39.8	39.6	39.8
R2	38.4	40.2	40.4	40.4	39.8	39.6	39.4	39.7
R3	38.3	40.3	40.1	40.3	39.9	39.9	39.5	39.9
R4	38.6	40.1	40.4	40.3	39.7	39.4	39.9	39.5
R5	38.2	40.7	40.6	40.5	40.0	39.8	39.9	39.9
R6	38.5	40.4	40.4	40.0	39.9	39.7	39.8	39.8
Mean	38.36	40.36	40.36	40.26	39.86	39.9	39.65	39.75
SD	0.1633	0.2160	0.1633	0.1862	0.1033	0.1789	0.2137	0.1506
SEM	±0.0667	0.0882	0.0667	0.0760	0.0422	0.0730	0.0872	0.0615
P value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

every hour for 1st to 6th hours, the temperature was 39.95°C, 39.60°C, 39.15°C, 38.61°C, 38.43°C and 38.61°C respectively. Finally, when a dose of 500mg/kg *Trigonella foenum* seeds extract was administered to pyretic rats, the initial rectal temperaturewas 38.58°C, after 18hours of yeast administration temperature rose to 40.40°C, then after every hour for 1st to 6th hours, the temperature was 40.60°C, 39.96°C, 39.53°C, 39.11°C, 38.91°C, and 38.26°C respectively.

The antipyretic effect of thehydro-alcoholic extract of *Trigonella foenum* seeds in rats given in table 4.1 showed that average initial rectal temperature of six rats was 38.90°C with SD of 0.48, SEM of ±0.19. After 18 hours

of yeast administration, the average rectal temperature was 40.40°C with SD of 0.54, SEM of 0.22. At 6th hours of extract administration (500mg/kg), the average rectal temperature was 38.26°C with SD of 0.19, SEM of ±0.08 with a very highly significant P-value of (<0.0001).

The antipyretic effect of the hydro-alcoholic extract of *Trigonella foenum* seeds in rats given in table 4.2 showed that average initial rectal temperature of six rats was 38.76°C with SD of 0.4227, SEM of ±0.1726. After 18 hours of yeast administration, the average rectal temperature was 40.48 with SD of 0.4875, SEM of 0.4875. At 6th hours of extract administration (250mg/kg), the average rectal temperature was 38.61°C with SD of 0.18, SEM of ±0.07 with a very highly significant P-value of (<0.0001).

Effect of Taraxacum officinale on temperature in yeast induced pyretic rats

The antipyretic effect of hydro-alcoholic extract of *Taraxacum officinale* leaves on Brewer's yeast induced pyrexia in rats given in table 5 showed that initial rectal temperature in control rats was 38.36°C, after 18 hrs of yeast administration, the temperature rose to 40.38°C, then after every hour for 1st to 6th hours, the temperature was 40.36°C, 40.26°C, 39.86°C, 39.90°C, 39.65°C, 39.75°C respectively (table 5). When a dose of 150 mg/kg paracetamol was administered to positive control rats, the initial rectal temperature was 38.38°C, after 18 hrs of yeast administration, temperature rose to 40.30°C then after every hour for 1st to 6th hours, the temperature was 39.88°C, 38.95°C, 38.85°C, 38.40°C, 38.13°C and 38.18°C respectively. Similarly, when a dose of 250mg/kg *Taraxacum officinale* leaves extract was administered to pyretic rats. The initial rectal temperature was 38.83°C, after 18 hrs of yeast administration temperature rose to 40.41°C, then after every hour for 1st to 6th hours, the temperature was 39.06°C, 39.78°C, 39.11°C, 39.18°C, 38.71°C and 38.50°C respectively. Finally, when a dose of 500mg/kg *Taraxacum officinale* leaves extract was administered to pyretic rats. The initial rectal temperature was 38.71°C, after 18 hrs of yeast administration, the temperature raised to 40.28°C, then after every hour 1st to 6th hours, the temperature was 39.81°C, 38.76°C, 38.83°C, 38.46°C,38.23°C and 38.35°C respectively.

The antipyretic effect of the hydro-alcoholic extract of *Taraxacum officinale* leaves in rats given in table 5.1 showed that average initial rectal temperature of six rats was 38.71°C with SD of 0.3189, SEM of ±0.1302. After 18hours of yeast administration, the average rectal temperature was 40.28 with SD of 0.2317, SEM of 0.0946. At 6th hours of extract administration (500mg/kg), the average rectal temperature was 38.35°Cwith SD of 0.32, with SEM of ±0.13 with a very highly significant P-value of (<0.0001).

The antipyretic effect of a hydro-alcoholic extract of *Taraxacum officinale* leaves in rats given in table 5.2 showed that average initial rectal temperature of six rats was 38.83°C with SD of 0.2733, SEM of ±0.1116. After 18 hours of yeast administration, the average rectal temperature was 40.41 with SD of 0.3601, SEM of 0.147. At 6th hours of extract administration (250mg/kg), the average rectal temperature was 38.50°C with SD of 0.20, SEM of ±0.08, with a very highly significant P-value of (<0.0001).

Effect of Salix alba on temperature in yeast induced pyretic rats

The antipyretic effect of hydro-alcoholic extract of *Salix alba* linn bark on Brewer's yeast induced pyrexia in rats given in table 6 showed that initial rectal temperature in control rats was 38.36°C, after 18hrs of yeast administration, the temperature rose to 40.38°C, then after every hour for 1st to 6th hours, the temperature was 40.36°C, 40.26°C, 39.86°C, 39.90°C, 39.65°C and 39.75°C respectively. When a dose of 150mg/kg paracetamol was administered to positive control rats the initial rectal temperature was 38.38°C, after 18hrs of yeast administration temperature rose to 40.30°C then after every hour for 1st to 6th hours, the temperature was 39.88°C, 38.95°C, 38.85°C, 38.40°C, 38.13°C and 38.18°C respectively. Similarly, when a dose of 250 mg/kg *Salix alba* bark extract was administered to pyretic rats, the initial rectal temperature was 38.56°C, after 18 hrs of yeast administration, temperature rose to 40.30°C, then after every hour for 1st to 6th hours the temperature was 40.51°C, 40.34°C, 39.58°C, 39.33°C, 39.11°C and 39.75°C respectively. Finally, when a dose of 500mg/kg *Salix alba*. bark extract was administered to pyretic rats, the initial rectal temperature was 38.76°C, 18hrs after yeast administration temperature rose to 40.25°C then after every hour for 1st to 6th hours, the temperature was 40.43°C, 40.41°C, 40.23°C, 40.03°C,39.85°C and 38.03°C respectively.

The antipyretic effect of the hydro-alcoholic extract of *Salix alba* linn bark in rats given in table 6.1 showed that average initial rectal temperature of six rats was 38.76°C with SD of 0.2658, SEM of ±0.1085. After 18 hours of yeast administration, the average rectal temperature was 40.25 with SD of 0.2258, SEM of 0.0922. At 6th hours of extract administration (500mg/kg), the average rectal temperature was 38.03°Cwith SD of 0.18, SEM of ±0.07 with a very highly significant P-value of (<0.0001).

The antipyretic effect of the hydro-alcoholic extract of *Salix alba* bark in rats given in table 6.2 showed that average initial rectal temperature of six rats was 39.36°C with SD of 0.4367, SEM of ±0.1783. After 18 hours of yeast administration, the average rectal temperature was 40.38 with SD of 0.2401, SEM of 0.0980. At 6th hours of extract administration (250mg/kg), the average rectal

temperature was 38.75°Cwith SD of 0.29, SEM of ±0.12 with a very highly significant P-value of (<0.0001).

Effect of Quepidol on temperature on Brewer's yeast induced pyretic rats

The antipyretic effect of hydro-alcoholic extract of Quepidol in rats given in table 7 showed that initial rectal temperature in control rats was 38.33°C, after 18hrs of yeast administration, the temperature rose to 40.32°C, then after every hour for 1st to 6th hours the temperature was 40.36°C, 40.26°C, 39.86°C, 39.90°C, 39.65°C and 39.75°C respectively. When a dose of 150mg/kg paracetamol was administered to positive control rats, the initial rectal temperature was 38.39°C, after 18hrs of yeast administration, temperature rose to 40.30°C then after every hour for 1st to 6th hours, the temperature was 39.88°C, 38.95°C, 38.85°C, 38.40°C38.13°C and 38.18°C respectively. Similarly when a dose of 250mg/kg Quepidol extract was administered to pyretic rats, the initial rectal temperature was 38.55°C, after 18hrs of yeast administration temperature rose to 40.28°C, then after every hour for 1st to 6th hours the temperature was 39.95°C, 39.78°C, 39.53°C, 39.33°C,39.57°C and 38.01°C respectively. Finally, when a dose of 500mg/kg Quepidol extract was administered to pyretic rats, the initial rectal temperature was 38.90°C, after 18hrs of yeast administration temperature rose to 40.16°Cthen after every hour for 1st to 6th hours the temperature was 39.58°C, 38.80°C, 38.91°C, 38.33°C,38.1°C and 37.56°C respectively.

The antipyretic effect of the hydro-alcoholic extract of Quepidol in rats given in table 7.1 showed that average initial rectal temperature of six rats was 38.90°C with SD of 0.48, SEM of ±0.19. After 18 hours of yeast administration, the average rectal temperature was 40.40 with SD of 0.54, SEM of 0.22. After 6th hours of extract administration (500mg/kg), the average rectal temperature was 37.5°C with SD of 0.04, SEM of ±0.02 with a very highly significant P-value of (<0.0001.)

The antipyretic effect of the hydro-alcoholic extract of Quepidol in rats shown in table 7.2 depicted that average initial rectal temperature of six rats was 38.55°C with SD of 0.39, SEM of ±0.16. After 18 hours of yeast administration, the average rectal temperature was 40.28 with SD of 0.2317, SEM of 0.0946. At 6th hours of extract administration (250mg/kg), the average rectal temperature was 38.1°Cwith SD of 0.12, SEM of ±0.04 with a very highly significant P-value of (<0.0001).

The antipyretic effect of Paracetamol on brewer's yeast induced pyrexia in rats given in the table 8 showed that average rectal temperature of six rats after 18 hours of yeast administration was 38.38°C with SD of 0.19, SEM of ±0.07. After 18 hours of yeast administration, the average rectal temperature was 40.05 with SD of 0.01, SEM of 0.04. At 6th hours of extract administration (250mg/kg), the average rectal temperature was 38.15°C with SD of 0.05, SEM of ± 0.02.

The control group receiving distilled water in rats given in table 9 showed that average initial rectal temperature of six rats was 38.36°C with SD of 0.1633, SEM of ±0.0667. After 18 hours of yeast administration, the average rectal temperature was 40.36 with SD of 0.2160, SEM of 0.0882. At 6th hours of distilled water administration, the average rectal temperature was 39.75°C with SD of 0.15, SEM of ±0.06 with a very highly significant p-value of (<0.0001).

DISCUSSION

The phytochemical screening of the hydro-alcoholic extract of *Achillea millefolium* leaves results in a positive test for alkaloids (++), flavonoids (++), saponins (++), tannins (++) and phenols (+). The average rectal temperature of rats after oral administration of 250 and a500mg dose of *Achillea millefolium* leaves at various time intervals are shown in table 3. The results showed that oral administration of 250 and 500mg/kg of *Achillea millefolium* decreased body temperature from 40.0°C and 40.16°C at one hour to 38.13°C ±0.1 and 38.00°C ±0.1 after the 6th hour of treatment respectively. The administration of 250 and 500mg/kg of plant extract decreased the temperature in the pyretic rats significantly (p<0.0001) respectively (table 3). These conclusions are in agreement with a study conducted by Vazirinejad *et al.*, (2014). They reported the antipyretic effect of *Achillea millefolium*. Furthermore, the results were also similar to the study of Benedek *et al.,* (2007), they confirmed that *Achillea millefolium* has anantipyretic effect. The phytochemical screening of the hydro-alcoholic extract of *Trigonella foenum*leaves was found positive for alkaloids (++), flavonoids (++), saponins (++), tannins (++) and phenols (++). The average rectal temperature of rats after oral administration of 250 and 500mg dose of *Trigonella foenum*seeds at various time intervals indicated that oral administration of 250 and 500mg/kg of *Trigonella foenum* seeds decreased body temperature 39.95°C, 40.60°C at one hour to 38.61°C±0.1, 38.26°C±0.1 after 6th hour of treatment respectively. The administration of 250 and 500mg/kg of plant extract decreased the temperature significantly (p<0.0001) at 6th hours of extract administration (table 4). This is in accordance with the study reported by Ahmadiani *et al.,* (2001). They reported that *Trigonella foenum-graecum* L. seeds have anti-inflammatory and antipyretic activities. These results are also similar to the reported study of Kaithwas *et al.*, (2011), in which they documented anti-inflammatory and antipyretic activities in the rat. Phytochemical screening of the hydro-alcoholic extract of *Taraxacum officinale* leaves was positive for alkaloids (++), flavonoids (++), saponins (++), tannins (++) and phenols (+). The average rectal temperature of rats after oral administration of 250 and 500 mg dose of *Taraxacum officinale* at various time

intervals was 39.06°C and 39.81°C to 38.50°C±0.1, 38.35°C±0.1 at one hour and after 6thhour of treatment respectively (table 5). The administration of 250 and 500mg/kg of plant extract decreased the body temperature in pyretic rats at 6thhour significantly ($p<0.0001$) as compared to the control group (table 5). These conclusions are in agreement with a study conducted by Jeon *et al.,* (2008) in which they reported the anti-inflammatory effects of *Taraxacum officinale* in rats. Phytochemical screening of the hydro-alcoholic extract of *Salix alba* bark revealed a positive test for alkaloids (+), flavonoids (++), saponins (++), tannins (++) and phenols (+). The average rectal temperature of rats after oral administration of 250 and 500mg/kg dose of *Salix alba* bark was 40.51°C and 40.43°C±0.1 at a1st hour and 39.75°C±0.1 to 38.03°C±0.1 at 6th hours respectively. The administration of 250 and 500mg/kg of plant extract decreased the temperature of pyretic rats at 6th hour significantly ($p<0.0001$) as compared to control group (table 6). The results are in agreement with that attained by Krivoy *et al.,* (2001). They reported that white yellow bark (*Salix bark*) contain a variety of chemical ingredients,the chief one calculated salicin which is metabolically transformed in the body as an antipyretic agent. Mehdi *et al.* (2012) reported the similar effect of *Salix alba*. Furthermore, they concluded that the active constituents of *Salix alba* (Salicin and salicylic acid) were widely used in the19th century by European physicians to treat rheumatic fever and as an antipyretic agent. *Salix alba* Linn bark extract contains phytosterols, glycosides, tannins, amino acids, phenolic compounds, carbohydrates and amino acids. The effect of the current study is also in agreement with the findings of Lakshman *et al*. (2006).

The initial rectal temperature of the rats after oral administration of different doses of Quepidol drug *(A. millifolium, T. officinale, T. foenum* and *S. alba*) at various time intervals shown in table 7 revealed that administration of 250 and 500mg/kg of Quepidol decreased the rectal temperature from 38.55°C±0.1, 38.90°C±0.1 at 1st hour to 38.01°C±, 0.1, 37.56°C± 0.1 after 6th hours of treatment respectively. Quepidol at the dose of 500mg/body weight produced a highly significant effect at the6th hour. The antipyretic effects could be due to cytochrome P-450 enzymes which are responsible for lowering fever. These results are in line with the earlier data that showed different herbal remedies and antipyretic drugs are a mixed fraction of compounds, chemically not related, however, share certain beneficial actions and helpful in lowering the temperature. The study showed that oral administration of Quepidol produces paracetamol like effect. Antipyretic agents from plants and herbs are important in the management of pyrexia. The current study showed that compound herbal preparation of Quepidol may be used in patients as it produced significant antipyretic effect compared to control group and plants extracts individually. However detailed pharmacological and phytochemical studies are still required to isolate the active constituents and their mechanism (s) of action.

CONCLUSION

The above discussed studies have clearly shown that Quepidol and plants extracts have exerted significant and consistent antipyretic potential in yeast induced pyretic albino rats. These results also suggested that plants contain some active chemical constituents (flavonoids or the alkaloid) that are responsible for its antipyretic actions against yeast induced pyrexia. Quepidol containing (*A. millifolium, T. officinale, T. foenum* and *S. alba* linn) has more potential than individual plants extract. The potential may be due to the synergistic effect of various constituents present in these plants, so the present study has supported the use of Quepidol and plants by herbal physicians. Yet, further study is needed to separate the active elements responsible for these activities and to reveal the exact mechanism(s) of action.

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