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TRANSMISSION OF HEPATOCURATIVE EFFECT OF *SPILANTHES ACMELLA* EXTRACT BASED GEL

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ABSTRACT: *Spilanthes acmella* (SA) commonly known as "Akarkara" frequently available in most of the areas of India, Sri Lanka, Bangladesh, China, Japan, and Thailand; is well reputed in the indigenous system of medicine for its medicinal use in toothache and rheumatic fever. The present study was aimed to evaluate its traditional use in liver diseases using the *in-vivo* model of rabbits. The *Spilanthes acmella* extract (SAE) based gel was investigated for its hepatocurative activities in Paracetamol intoxicated (2 g/kg) rabbits. Rabbits were divided into three groups, normal control (saline-treated) hepatotoxic control (Paracetamol treated) and remaining one was hepatotoxic treated with the SAE -based gel (400 mg/kg) for 7-14 days. One serving as control another as hepatotoxic and last one as treated with Paracetamol and then SAE-based gel Group 2nd and 3rd were intoxicated with Paracetamol. After the 3rd day of the treatment with Paracetamol, increased serum transaminases (sGOT and sGPT) and alkaline phosphatase (ALP) levels were observed. In the case of hepatocuration of SAE -based gel caused a significant reduction in all the above serum markers for liver functioning. These data and histopathological study suggest that the presence of the hepatocurative constituents in SAE -based gel rationalizes its medicinal use in liver dysfunction.

INTRODUCTION: The World Health Organization has assessed that about 80% of the population in developing countries are unable to afford drugs and trust in traditional medicines especially those that are plant-based [1, 2].

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Herbal medicines have been utilized for many purposes, particularly in medical care as anti-asthmatics (86.79%), anti-rheumatics (62%) [8], diuretics (60.22%), anti-inflammation (29.62%), anti-cancer (9.75%), anti-diabetics (8.33%), anti-microbial, anti-fungal, anti-oxidants, anti-allergy, analgesics, anti-obesity and anti-hyper-tension [3, 4].

Our concern centers on medicinal plants bearing bioactive compounds, which are employed as therapeutics and healthcare [5]. Therefore, *Spilanthes acmella* Murr. is a plant of great interest owing to its known reputation as an anti-toothache plant and

hold tremendous medicinal usages. It is an annual or short-lived herb that is 40-60 cm tall. It is grown in damp area [1, 6]. The plant species has been used commonly as a folk remedy, *e.g.*, for toothache, rheumatic and fever [6], like fresh vegetable [1] as well as a spice for Japanese appetizer [7]. The constituent like spilanthol is found in often called toothache plants like *Spilanthes acmella* due to the analgesic effect [1, 8, 9, 10, 11, 12].

Like other alkamides, spilanthol is an amphiphilic compound with a relatively polar amide and a less polar fatty acyl and known for traditional remedies throughout the world. Also, it can be extracted from plants using either methanol, ethanol, supercritical CO_2 or hexane [9, 13, 14, 15, 16] as our study based on. Extract of *Spilanthes acmella* in methanol. The aerial parts of *Spilanthes acmella* contain spilanthol are used as a spice [10, 17] which have anti-bacterial activity also. This study data from literature confirmed and validated our results.

Further, literature also supports our formulation of SAE -a based gel that can be absorbed through the skin, endothelial gut, oral mucosa and blood-brain barrier [18, 19]. *S. acmella* Murr. has been used as a traditional medicine for various diseases. Bioactive metabolites were found in aerial parts, leaves, flowers, and whole plants of *S. acmella* Murr and extracts have been shown to exhibit antioxidant activities [20].

The gel is semisolid viscous preparation having an alcoholic base. It tends to melt at body temperature and dried after applying to the skin. Gels can be used in a wider and protect the APIs from the external environment and also used to treat allergies [21]. Active molecules entrapped in the gels can be removed easily as compared to other dosage forms like creams and ointments [22].

EXPERIMENTAL:

Materials: Following chemicals with specified sources were used for experimental procedures; methanol (Merck, Germany), Paracetamol® was gifted by Askari Pharmaceuticals (Lahore, Pakistan). Deionized water was used for the dilution of various samples. Jatepar® was obtained from Sami (Pvt. Ltd., Pakistan). Benzyl alcohol, carbopol-940, *Spilanthes acmella* (SAE) extract, ethylene glycol, PEG-1000. All the chemicals used were of analytical grade.

Apparatus: Vacuum pump (Vacuum brand, Germany), Rota-vapor (Buchii, Japan), Analytical electric balance, accuracy ± 0.l mg (Diamond MCT 500), Sonicator (Ney Ultra Sonik, Korea), Deionizer water plant (Waterman, Karachi, Pakistan). Pestle and mortar (Glass Made), desiccators, beakers of different volumes 50 ml and 100 ml, graduated cylinder 50 ml and 100 ml.

Serum Parameters: Serum glutamic oxalo-acetic acid transaminase (sGOT), serum glutamic pyruvic transaminase (sGPT) and alkaline phosphatase (ALP) levels were evaluated by enzymatic kits (Sigma Co.,) using spectrophotometer (Perkin Elmer UV 256).

Animals: Male rabbits of local breed (*Oryctolagus cuniculus*) and either sex weighing 1-1.5 ± 0.2 kg were used. All animals were housed at the animal house of Department of Pharmacy Bahauddin Zakariya University, Multan. Animals were in stainless steel cages under standard laboratory conditions, green fodder and water were available at the laboratory.

Collection and Extraction of Plant Material: The Whole plant of *Spilanthes acmella* was purchased from Herbal store of the local market of Multan (Pakistan). The plant was identified with the help of expert Taxonomist (Dr. Zafarullah) from the Institute of Pure and Applied Biology, Bahauddin Zakariya University, Multan (Ref.no.96-2016/ BZU.PHM). The plant material was rendered free from soil and adulterated materials, shade dried at 40 °C and then ground in electric grinder into a coarse powder which was then soaked into methanol for 72 h with occasional shaking. The soaked material was rendered free of plant debris by passing through a muslin cloth, and the fluid portion was filtered through a fine filter paper.

The filtrate was preserved in a labeled glass bottle with a tight cap. The residue was again soaked in methanol for 72 h. The soaked material was rendered free of plant debris by passing through a muslin cloth, and the fluid portion was filtered through a fine filter paper. All portions of filtrate were combined and subjected to evaporation under reduced pressure on a rotary evaporator to a thick paste-like a mass of dark brown color, *i.e.*, the crude methanolic extract (SAE). The extract was

poured into a petri dish and placed in desiccators for 6-8 h so that the remaining solvent must be evaporated. Dried extract of the plant was transferred in already weighed bottle. Final extract was dissolved in distilled water for all *in-vitro* experiments. The remaining extract was preserved in the refrigerator for further processing.

Preparation of Optimized *Spilanthes acmella* Extract- Based Gel: In preparation of gel, first of all, 2.5 g carbopol-934 was dissolved in the 35g propylene glycol (PG) with the help of magnetic stirrer (solution A). Then 25 ml methanol was taken and dissolved in the 5 g polyethylene glycol (PEG-1000) and 0.25 g menthol crystals are added in it by continuous stirring (solution B). Quantity sufficient of double distilled water was taken in the conical flask and 1 gm *Spilanthes acmella* extract (SAE) was dissolved in it by stirring (solution C). Then mixed this drug solution C into solution B mixture together and this combination was slowly added in the solution A *i.e.* carbopol mixture with continuous stirring until all materials were mixed homogeneously. Then 20 ml of benzyl alcohol was added in it continuous stirring, and 0.55 ml ethylene glycol was mixed in it. Then adjusted pH by pH meter (at 5-6) by TEA and the final volume was adjusted with the help of water at 100ml as is given in **Table 1**. The *S. acmella* extract-based gel was thoroughly stirred until desired consistency was developed and kept aluminum tubes for future use.

TABLE 1: FORMULATION OF *SPILANTHES ACMELLA* EXTRACT GEL

Ingredients	Amount
Spilanthes acmella extract	1.0 g
Carbopol 934	2.5 g
Benzyl alcohol	20 ml
Propylene glycol	35.0 ml
PEG-1000	5 g
Triethanolamine (TEA)	2.3 ml
Ethylene glycol	0.55 ml
Menthol crystals	0.25 g
Methanol	25 ml
Double distilled water	Q.S. 100 ml

Evaluation of *Spilanthes acmella* Extract-Based Gel: The following physical parameters were performed to evaluate the formulated gel.

pH Measurements: pH meter's electrode was introduced in gel and note down the pH readings by using the Digital pH meter (PHS-3E). This practice was done three times and got its pH.

Viscosity Measurements of Gels: The readings are noted on the screen of the Viscometer (Viscometer (NDJ-8S), by applying the spindle S63 in the gel; its speed of rotation was almost 0.6 rpm. The gel was settled at room temperature (25 °C ±1) after 30 min. This process was performed three times, and at the end calculated the mean viscosity.

Homogeneity: Visually gel was tested that there were no lumps/aggregates as in **Table 2**. The gel was clear fully check by the naked eye to confirm homogeneity.

Spreadability Test: Spreadability was determined by in-house made wooden block apparatus [23], having fixed a pulley at one end and measurement was done by "slip" and "drag" physiognomies of the gel. Sandwiched 1-2 g of gel on focal point already centrally marked on a ground glass slide (5×2 cm length × width) fixed on the wooden block and pressed the second glass slide over it. Then putting weight (100 g) on the upper glass slide for five minutes to exorcize air and to make a uniform film of the gel between the slides. Excess of the gel was scrapped off from the edges. The upper plate was then allowed to a pull of 20 g weight with the help of a string attached to the hook and the time in seconds by the top slide to cover a distance of 7.5 cm was observed. A shorter interval indicates better spreadability [24]. The spreadability was calculated by using the formula:

$$S = M \times L / T$$

When M is weight (g) tied to upper slide, L is length (cm) of glass slides, and T is time (s) taken for spreading the gel between glass slides. Determinations were made in triplicates.

Skin Irritation Test: Gel (1 g) was smeared (2 Sq. Inch) on human volunteers forearm for 3 h and observed the irritation, itching, rashes/redness and lesion [25].

Accelerated Stability Studies: Gel was retained instability chamber for almost two (02) months according to ICH standards. The temperature of the chamber was maintained at 40° ± 2 and humidity was almost 75 ± 4 percentage: observed pH value and physical appearance for 2 months.

Statistical Analysis Microsoft Excel, 2013 has been used for statistical analysis of data *i.e.* mean

and standard deviation calculation. The use of ***showed the level of significance (***p<0.001) determined with the help of One-way ANOVA followed by Dunnet's test. Arrows indicated the relative comparison of the respective sets in data. The differences between physical parameters of gel had been determined by multiple regression analysis (MLRA) and analysis of variance (ANOVA) at p<0.05.

Hepatocurative Activity: For the assessment of the hepatocurative activity of the SAE-based gel on rabbits of local breed and were divided into three experimental groups each comprising on five rabbits, one serving as normal control (saline-treated), the other as hepatotoxic control (Paracetamol (2 g/kg) treated), and the last one was receiving 400 mg/kg body weight of SAE-based gel respectively topically. Blood samples were taken at 7th and 14th day to determine the serum levels of transaminases (ALT, AST) and alkaline phosphatase (ALP) being the biochemical markers of hepatic status. Blood samples were taken at 7th and 14th day to determine the plasma levels of ALT, AST, and ALP.

Histopathological Study: Histopathological studies of rabbit liver, used in the *ex-vivo* study, was done to determine its fate after absorption of the drug through it [26]. The slides of different portions of liver tissues were made and stained with hematoxylin and eosin and then compared with the slides of normal liver tissues to observe the changes in the liver through optical microscope [27].

RESULTS AND DISCUSSION:

Evaluation of *Spilanthes acmella* Extract-Based Gel: The pH determined was 5.7 ± 0.02 while viscosity was calculated 1871 ± 0.01 (cP). Gel tested showed no lumps/aggregates and appearance was clear. There was no irritation, itching, rashes/redness and lesion observed in any of the volunteers. The spreadability was determined 6.45 ± 0.01 g.cm/s are indicating that gel is more easily spread by applying a small amount of shear stress **Table 2**.

TABLE 2: THE RESULTS FOR ACCELERATED STABILITY FOR *SPILANTHES ACMELLA* EXTRACT-BASED GEL

pH mean ± SD n=3			Viscosity Mean (cP) ± SD n=3			Homogeneity			Spreadability mean (g.cm/s) ± SD n=3		
0M	1M	2M	0M	1M	2M	0M	1M	2M	0M	1M	2M
5.7 ± 0.02	5.69 ± 0.01	5.69 ± 0.017	1871 ± 0.02	1863 ± 0.018	1862 ± 0.019	Good/ Clear	Good/ Clear	Good/ Clear	6.45 ± 0.01	6.42 ± 0.01	6.40 ± 0.02

TABLE 3: HEPATOCURATIVE EFFECT OF THE *SPILANTHES ACMELLA* BASED GEL ON BT, AST, ALT AND ALKALINE PHOSPHATASE LEVELS

Treatment	BT	ALT	AST	ALP
At 0 day sampling	0.54 ± 0.05*	24.71 ± 7.11***	26.14 ± 12.64*	56.85 ± 28.82**
Paracetamol treated after 3rd day sampling	0.71 ± 0.09*	37.14 ± 12.91***	34.43 ± 14.63*	53.86 ± 11.80**
Extract treated after 7th day sampling	0.66 ± 0.13*	30.28 ± 6.18***	21.14 ± 3.84*	48.57 ± 20.16**
Extract treated after 14th day	0.67 ± 0.11*	14.29 ± 2.43***	18.57 ± 2.30*	15.01 ± 1.73**

Note: ***Significant at 0.001, ** Significant at 0.01 and *Significant at 0.05. Values represents Mean ± S.E.M (n=5).

Hepatocurative Effect of *Spilanthes acmella* Based Gel in Hepatotoxic Rabbits: Paracetamol significantly (p<0.001) raised the respective levels of serum transaminases (sGOT, sGPT) and alkaline phosphatase (ALP), when compared with these, were compared with saline-treated groups **Table 1**. Moreover, when Paracetamol induced hepato-toxicity was challenged with SAE gel, it not only significantly (p<0.001) reduced the toxic effects of Paracetamol in rabbits but also exhibited that its chronic treatment of SAE gel has more capacity and is beneficial for hepatocuration as described in **Table 3** and *Spilanthes acmella* SAE has more reduced the toxic effects of Paracetamol. In this study, hepatocurative activities of newly formulated SAE-based gel have been assessed; Paracetamol was used for intoxication of the liver as Paracetamol causes the liver injury at higher doses by raising levels of the relevant serum markers of liver functioning [28]. The elevation of sGOT, sGPT, and alkaline phosphatase are indicative for the release of enzymes from disrupted cells. Treatment with methanolic extract of the aerial parts of the *Spilanthes acmella* based

gel (certainly due to the presence of spilanthol) significantly reduced the raised levels of sGOT, sGPT and alkaline phosphatase in paracetamol induced-hepatotoxic rabbits. This showed the presence of constituents in SAE-based gel responsible for the liver regeneration which in turns reduced the raised enzyme level of the liver due to paracetamol intoxication. Wu *et al*., 2008; Hernández *et al*., 2009; Dias *et al*., 2012 supported our results due to the anti-inflammatory activity of constituents in SAE-based gel. This data showed the successful use of SAE-based gel in liver dysfunction, and these results are in hasty for its traditional use in liver disorders.

Histopathological Study of Pre- and Post-use Liver Tissues: The slides of different portions of normal rabbit liver tissues were made during the study, stained with hematoxylin and eosin and observed microscopically under high magnification as shown in **Fig. 1**. As evident from **Fig. 1A**, there was hepatocytes normal and no inflammation in portal triade. Some observation of fatty changes were noted which are sometimes presents in normal body cells. **Fig. 1B** is indicating pycnotic nuclei (condensation of nuclei) and inflammation changes in a central vein.

There were prominent fatty changes however, hepatocytes/fibroblast observed normal and also observed inflammatory changes in portal triade. The pycnotic area along fatty change observed and more fatty changes observed along karyolysis, indicating necrosis in the nucleus. **Fig. 1C** and **D** showed extensive lymphocytes and fibroblast with inflammation cells with monocytes (engulfment) however, inflammatory cells suggested absorption level increased. This meant good changes in progress due to applied SAE based gel and in general, slides showed inflammatory cells changes where extensive lysis of nucleus was seen further, morphological changes magnified.

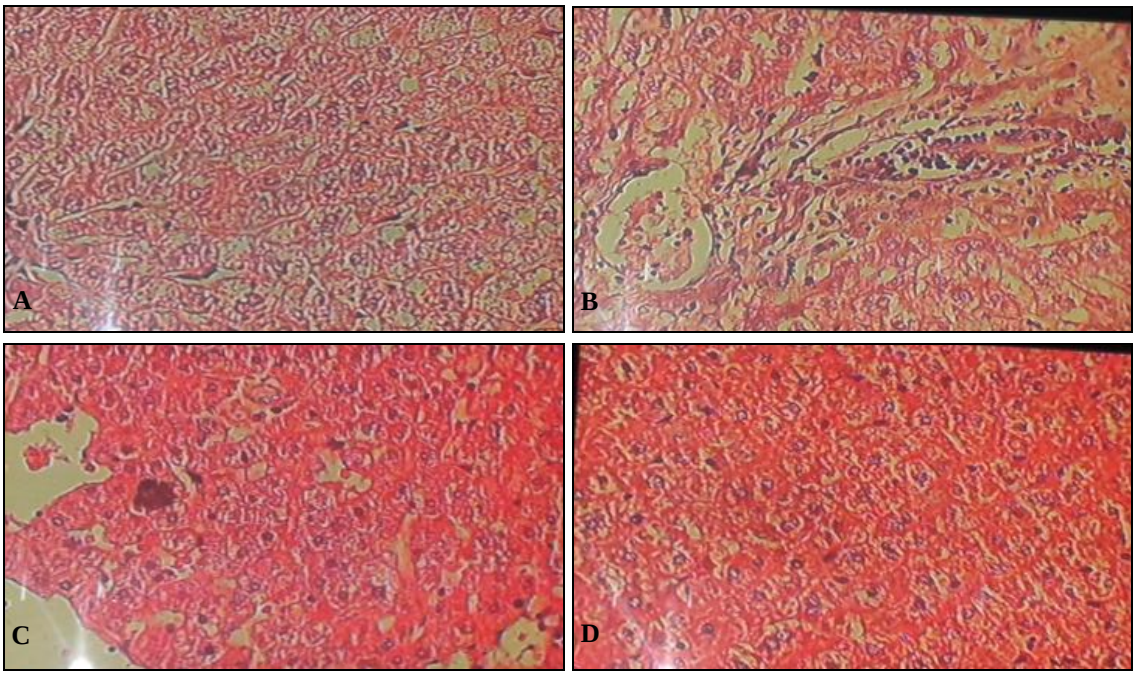

FIG. 1: HISTOPATHOLOGICAL EXAMINATION OF RABBIT LIVER TISSUES DURING WHOLE STUDY PERIOD. A) Control liver tissue slide showing normal hepatocytes and no inflammation in portal triads. However, some observations of fatty change present in normal body cells usually. B) Toxic liver slide is showing pycnotic nuclei (condensation of nuclei) and inflammation changes in a central vein. Fatty changes are prominent, and hepatocytes/fibroblast was observed normally. There were inflammatory changes in portal triads and the pycnotic area along fatty change observed with karyolysis, indicating necrosis in the nucleus. C) G-1 is the treated slide of the liver after initial day applying SAE based gel which showed Extensive lymphocytes and fibroblast with inflammatory cells and monocytes (engulfment). Inflammatory cells evoked absorption levels were increased with good change and progressive; however, extensive lysis of nucleus and inflammatory cells were seen. D) G-2 is the treated slide of the liver after applying gel which showed morphological changes magnified.

CONCLUSION: Experimental findings of this study showed the simulation of hepatocurative effect from the crude extract of *Spilanthes acmella* based gel. It may due to the presence of such components in *Spilanthes acmella* (SAE) is well reputed for its traditional uses in liver disorders.

Approval by Ethics Committee: The approval for *ex-vivo* studies in animals and human volunteers were taken from the "Ethical Committee" (ref no. 102-2017/BZU.PHM) of Faculty of Pharmacy, B. Z. University Multan.

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CONFLICT OF INTEREST: The authors declare that there is no potential conflict of interest associated with this study.

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