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Original Article

Evaluation of Balya Activity of Atibala (*Abutilon indicum* (Linn.) Sw) in Cisplatin-Induced Muscle Atrophy Model

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ABSTRACT

Background: Cisplatin, an antineoplastic drug, induces muscle atrophy in patients. Given this, investigating potential interventions such as nutritional supplements or medications to regulate catabolic processes, cellular damage and inflammatory responses emerges as a promising strategy for restoring muscle mass and strength. Drawing from the rich tradition of *Ayurveda, Atibala* (*Abutilon indicum* (Linn.) Sw) is noted in the *Balya Dashemani* of *Caraka* Samhita for its reputed role in promoting muscle bulk and strength. In light of this, we undertook the present study to evaluate the potential of *Atibala* root decoction in enhancing health and counteracting muscle weakness induced by cisplatin in Wistar rats. **Objectives:** The primary aim was to evaluate the health-promoting (*balya*) activity of *Atibala* (*Abutilon indicum* (Linn.) Sw) in an animal model. Additionally, we sought to assess its effectiveness in countering cisplatin-induced muscle weakness in the same animal model. **Materials and Methods:** 32 male Wistar rats, each weighing 150-200 g, were divided into five groups. Muscle weakness was induced by intraperitoneal injections of cisplatin on days 1, 8 and 15. Atibala Kashaya was administered daily. Muscle mass, strength, body weight, thigh circumference, running time on the rotarod, distance traveled in the actimeter and serum cortisol levels were assessed. Gastrocnemius muscle histopathology was also examined upon sacrifice at the end of the study. **Results:** Histopathological analysis revealed improved muscle growth in the *Atibala Kashaya*-treated groups. While no significant differences were observed in serum cortisol, rotarod and actimeter parameters between the groups, a mean difference was noted on Day 15 and Day 45. Significant improvements in weight and thigh circumference were found when analyzed within all groups.

Keywords: Atibala, Balya, Cisplatin, Muscle Atrophy, Weakness.

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INTRODUCTION

The decline in muscle mass, structure, strength and stamina is associated with various factors such as ageing, inactivity, diseases like Parkinsonism and hemiplegia and the use of anti-cancer drugs like cisplatin. In addition, under these circumstances, there is minimal protection to tissue damage.[1] Sedentary lifestyles, prolonged bed rest, space travel and hindlimb suspension can pose challenges for skeletal muscles, leading to issues such as abnormalities in microcirculation, muscle wasting, protein depletion, alterations in contraction characteristics and shifts in fibre types. Unloading causes skeletal muscles in both young and old to experience elevated oxidative stress; this phenomenon may be a key factor in the onset of muscular atrophy. When skeletal muscles are unloaded, the number of myonuclei decreases and the number of apoptotic myonuclei increases at the same time.[2] The side effects of chemotherapy further exacerbate the situation by reducing physical activity, limiting treatment options, increasing morbidity and impairing the quality of life for patients.[3]

Cisplatin is a potent chemotherapy medication widely utilized for treating diverse cancer types, such as those affecting the neck, bladder, head, lung, ovaries and testicles. Cancer patients undergoing cisplatin treatment commonly experience primary side effects, notably muscle weakness and fatigue, resulting from the depletion of skeletal muscle mass.[4] The muscle dysfunction induced by cisplatin involves intricate mechanisms, encompassing alterations to the ubiquitin-proteasome system, autophagy and the Insulin-like Growth Factor-1 (IGF-1)/PI3K/Akt pathway.[5]

Various culinary and therapeutic substances have been used for a variety of purposes throughout history, including nutrition. The word "Balya" in Ayurveda refers to a variety of practices used to improve general body mass, immunity and strength. According to Caraka Acarya, the maintenance of good health is intricately tied to one's bala. Broadly speaking, any activity that contributes to an individual's strength is classified as "*Balya*." The evaluation of Bala is conducted through Vyayamashakti, which refers to

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the ability to engage in exercise, indicating overall working capability.[6]

Acarya Caraka systematically classified medications based on their pharmacological properties, organising them into 50 categories known as Mahakashayas. Among these, the Balya Mahakashaya is detailed in the 4th chapter of the Carak Samhita Sutra Sthana. This category comprises 10 drugs: Aindri, Rishabhi, Atirasa, Rishyaprokta, Payasya, Ashvagandha, Sthira, Rohini, Bala and Atibala. The term "*Balya*" refers to elements that increase physical vigour and strength.[7]

According to both Caraka and Sushruta Samhita, the potency of these strength-enhancing drugs is attributed to the "Madhura" taste.[8] Historical evidence of Atibala's usage traces back to the Vedic period, persisting through the Samhita and ancient Nighantu periods to contemporary texts. Post-medieval era, various formulations of Atibala have been documented in Samhitas and Nighantus, identified under titles such as Baladvaya, Balatraya, Balachatushtaya and Balapanchaya, denoting two, three, four and five varieties of the plant, respectively.[9]

The herb Atibala (*Abutilon indicum* (Linn.) Sw) is renowned for its immunomodulatory and antioxidant properties.[10] It works well as a supplement for vataja illnesses, including cervical spondylosis, facial palsy, paralysis and more.[11] This study aims to evaluate the potential effects of Atibala root decoction on muscular strength, size and recovery through experimental investigations. There are two primary sections to the study. In the first section, we explore the promotional aspect of Atibala Dravya. Subsequently, we observe the curative and therapeutic approach of Atibala Dravya to cisplatin-induced muscle weakness in Wistar rats. The parameters for assessing structural changes include weight and thigh circumference, while functional activity is measured using Rotarod and Actimeter instruments. Additionally, serum cortisol readings are included as part of the biochemical investigation.

MATERIALS AND METHODS

Materials

After approval of Institutional Animal Ethical clearance (BMK/IAEC/Res.No.21/2021-05), an experimental study was conducted at the CPCSEA-registered Animal house, KAHER's Shri B.M.K. Ayurveda Mahavidyalaya, Belagavi. CPCSEA rules were followed in the study.

Chemicals

Inj. Cizcan 5 mg/kg body weight (Cisplatin) was purchased with the prescription of a Hematooncologist from a local pharmacy. [TM of Baxter, Batch No. 1331123, Expiry Date: 04/2024].

Source and Authentication of raw drugs

The raw drug roots of Atibala (*Abutilon indicum* (Linn.) Sw) were collected from the natural habitat of Badami taluk in Bagalkot District of Karnataka. The collected drug was authenticated in AYUSH-approved ASU DTL, Central Research Facility, KAHER's Shri B M K Ayurveda Mahavidyalaya, Belgavi and ICMR-NITM, Belagavi [RMRC-1672].

Quality Control and Testing

The quality control analysis of raw drug Atibala mula and freshly prepared kashaya was carried out by following standard methods as per the Ayurvedic Pharmacopoeia of India Guidelines and analysed at AYUSH-approved DTL for ASU Drugs of KAHER'S Shri BMK Ayurveda Mahavidyalaya in Belagavi. Fresh Atibala Kashaya Yoga was prepared as per Sharangadhara reference and with SOP.[12]

Methodology

Experimental animals

32 healthy adult male Wistar rats, weighing between 150 and 200 g, were procured from Shri Rajendra Enterprises (841/bt/04/CPCSEA) and accommodated in cages, where they acclimatised for a week. During this period, they were provided with a standard diet and water was made available ad libitum. After the acclimatisation phase, the animals were divided into five groups, each consisting of six animals, except for Group C, which had eight animals.

Experimental Study Design (Table 1)

All rats received a regular pellet diet and drank water daily for 45 days.

On the 15th day, four animals from Group C were sacrificed and studied.

Dose of Atibala Mula Kashaya Yoga in Humans: 1 pala (48 mL)/day.

Animal Dose: According to Paget and Barnes' conversion factor (1964), the dose conversion from humans to rats is calculated to be 0.018.[13]

For rats weighing around 200 g, the calculated dose will be 48 multiplied by 0.018= 0.864 mL.

Parameters of an Experimental Study

Continuous clinical observations were conducted throughout the study, monitoring all animals for changes in skin condition, fur quality, food intake and water intake. These observations were recorded on a daily basis. The body weight of each rat was documented at weekly intervals. Additionally, the thigh circumference of the right hind limb was measured on days 0th, 15th and 45th. To measure thigh circumference, the right hind limb was stretched and a measuring tape was wrapped around the thigh region. Blood samples were obtained through retro-orbital puncture using a capillary tube on the 0th, 15th and 45th days and collected into labelled 2 mL vials for serum cortisol measurement.

The blood samples were sent to the Jeevan Diagnostic Centre in Belgavi.

Histopathology

After sacrifice, the Gastrocnemius muscle was dissected, washed, kept in 10% formalin and sent for histopathology analysis to Jawaharlal Nehru Medical College, Pathology Department, Belagavi. Gastrocnemius muscle samples were embedded in paraffin and stained with hematoxylin and eosin dye. Subsequently, all sections were examined using an OLYMPUS microscope under 10x and 40x magnification.

Rotarod Test

The rotarod test stands out as the most sensitive method for screening drugs intended to enhance muscular strength. Rotamex (Columbus Instruments), equipped with automatic timers and falling sensors, was employed for this purpose. The duration each animal spent on the rod was automatically recorded and the average performance over three consecutive attempts was measured. The running time of each rat was considered a reliable indicator of muscle strength. The latency to fall was automatically recorded through photocells.

Actimeter Analysis

The experiments were conducted using the Opto-Varimex-5 system with Auto-track v4.96 software from Columbus Instruments. Each rat was placed in the system for a 5 min time period. The actimeter was utilised to individually record the spontaneous locomotor activity of each animal.

The equipment was set up in a soundproof and well-ventilated room during the testing phase. The activity counts were quantified in arbitrary units, calculated based on the number of beam breaks resulting from the animal's movement.

Statistical Analysis

All data are presented as mean±S.D in tables and graphs. Statistical analyses were conducted using the GraphPad Prism 5 software. For within-group analysis, a paired *t*-test was employed, while for between-group analysis, an independent *t*-test was utilised.

RESULTS

General Observations

The skin of rats in the induction groups exhibited flaccidity. In the Normal and Atibala Kashaya groups, the skin appeared firm. Induction groups experienced shedding of body hair, diminished lustre and reduced activity. Following the administration of Atibala Kashaya, a notable improvement was observed in the skin, fur and activity of cisplatin-treated rats.

Effect of Atibala Kashaya on Body Weight and Thigh Circumference on the 45th Day

Significant results were observed within the groups (Table 2). While between-group results are statistically insignificant, notable mean differences in weight and thigh circumference are evident on the 45th day (Table 5).

The weight on the 45th day of the cisplatin group was [283.3±40.27] and that of the parallel Atibala Kashaya-treated group was [297.5±41.49].

Table 1: Animal Study Design.

Groups	Intervention	Route
Group A (Normal Group) N=6.	-	Orally
Group B (Test Drug-*Kashaya*) N=6.	*Atibala Mula Kashaya* for 45 days.	Orally
Group C (Induction) N=8.	Cisplatin (1st, 8th and 15th day).	Cisplatin-IP (5 mg/kg body weight).
Group D (Trial Group I-Induction+*Kashaya* after 15 days) N=6.	Cisplatin (1st, 8th and 15th day) and *Atibala mula Kashaya* after induction from day 16 to day 45.	Cisplatin- IP (5 mg/kg body weight) *Atibala mula Kashaya* Orally.
Group E (Trial Group II-Induction+*Kashaya*-Parallel treatment) N=6.	Cisplatin (1st, 8th and 15th day) and *Atibala mula Kashaya* for 45 days.	Cisplatin-IP (5 mg/kg body weight) *Atibala mula Kashaya* orally.

Table 2: Comparison of Changes in body weight (g.) and Thigh circumference (cm.) within groups represented as mean±SD with percentage difference between 15th day and 45th day.

Within Groups	A				B				C			D			E		
Days	0th	15th	45th	%	0th	15th	45th	%	15th	45th	%	15th	45th	%	15th	45th	%
Weight	208.2± 21.71	246.2± 21.96	348.6± 28.08***	34.43	240.0± 33.06	-	395.8± 19.70**	49.009	239.5± 8.851	283.3± 40.27	16.75	199.5± 29.92	261.5± 50.92*	26.898	225.5± 20.77	297.5± 41.49**	27.53
Thigh circumference	4.460± 0.4561	246.2± 21.96	5.260± 0.1817*	16.46	4.700± 0.2449	-	5.625± 0.2986**	17.91	4.250± 0.2887	4.750± 0.2887	11.11	4.033± 0.08165	4.767± 0.4590*	16.68	4.183± 0.1602	4.850± 0.4231**	14.76

*p<0.05, **p<0.01, ***p<0.001.

Table 3: Comparison of Changes in Serum cortisol (ng/mL) within groups represented as mean±SD.

Serum Cortisol (ng/mL)		A	B	C	D	E
Within Groups	0th	38.58±13.22	40.325±15.21	33.40±13.78	28.73±2.170	27.23±2.328
	45th	13.12±4.513**	11.88±3.561*	10.53±2.869*	10.35±1.948***	9.719±2.925***

*p<0.05, **p<0.01, ***p<0.001 compared to normal.

Table 4: Comparison of Changes in Running time of Rotarod (sec.), Ambulatory duration (sec) and distance (inch) travelled in Actimeter within groups represented as mean±SD.

Within Groups	A			B		C		D		E	
Days	0th	15th	45th	0th	45th	15th	45th	15th	45th	15th	45th
Rotarod	41.39± 4.989	45.27± 9.882	49.99± 7.789	36.26± 5.122	52.43± 14.66	40.84± 7.022	39.41± 11.87	45.73± 14.34	49.02± 9.246	49.02± 9.246	51.44± 17.54
Ambulatory	100.54± 17.01582	186.80± 50.0463	211.78± 45.76544**	105.675± 11.32766	189.875± 45.76544*	104.2± 11.01000	104.4± 48.21860	71.08333± 27.69277	96.11667± 46.08351	54.3667± 45.88718	78.61667±42.35717
DIZ	606.0± 328.8	1953± 1015	3148± 1480*	636.8± 418.9	2031± 218.6**	954.5± 345.3	784.4± 148.3	384.4± 302.4	746.3± 467.5	224.8± 233.9	633.2± 960.3

*$p<0.05$, **$p<0.01$, ***$p<0.001$ compared to normal.

The thigh circumference on the 45th day of the cisplatin group was [4.750±0.2887] and that of the parallel Atibala Kashaya-treated group was [4.850±0.4231].

Effect of Atibala Kashaya on Serum Cortisol on the 45th day The within-group comparison revealed a significant difference in serum cortisol levels across all groups (Table 3). However, the between-group results were found to be statistically insignificant (Table 1). It is worth noting that in the first three groups, the standard deviation was higher due to the extreme values observed in 1-2 rats. This elevated value may be attributed to initial physical stress during handling, which cannot be entirely ruled out. Nevertheless, the study drug undeniably plays a role in modulating cortisol levels, as may be reflected in the histopathological findings.

Effect of Atibala Kashaya on the running time of the rotarod, ambulatory and distance travelled by the actimeter.

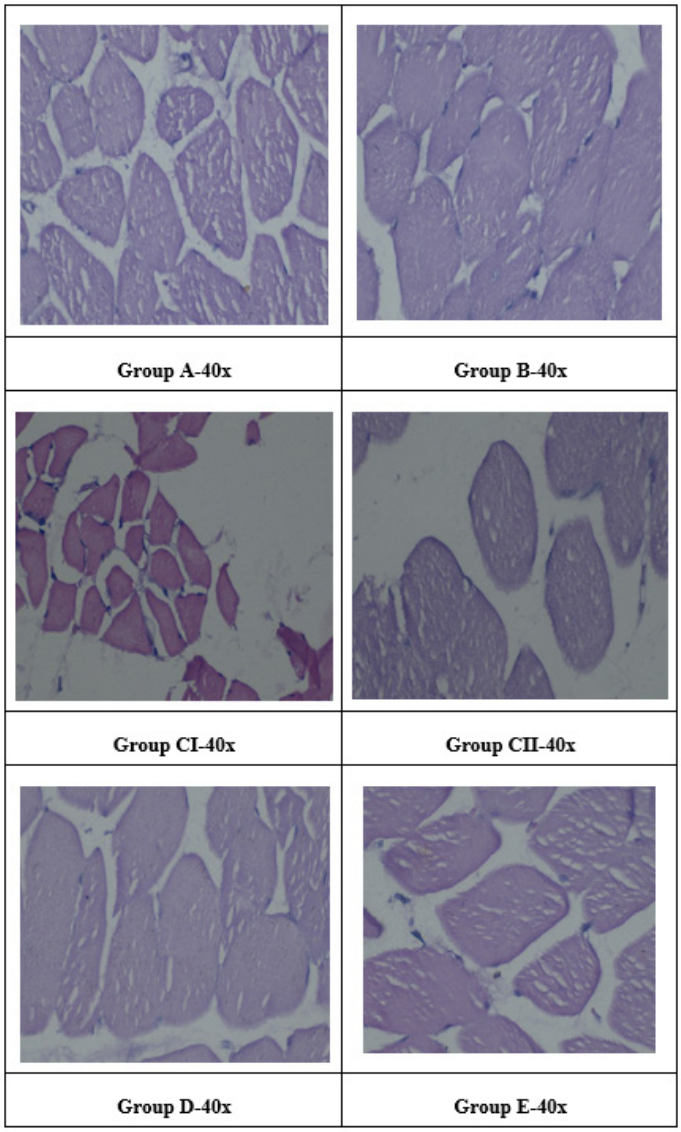

Figure 1: Histopathology of Gastrocnemius muscle.

Table 5: Comparison of changes in Weight (g.), Thigh Circumference (cm.), Serum Cortisol (ng/mL), Running time of Rotarod (sec.) and ambulatory duration (sec) and distance (inch) travelled in Actimeter on 45th day between the groups represented as mean±SD.

Between Groups	A to B		A to C		C to D		C to E		D to E	
	A	B	A	C	C	D	C	E	D	E
Weight	348.6± 28.08	395.8± 19.70	348.6± 28.08	283.3± 40.27*	283.3± 40.27	261.5± 50.92	283.3± 40.27	297.5± 41.49	261.5± 50.92	297.5± 41.49
Thigh circumference	5.260± 0.1817	5.625± 0.2986	5.260± 0.1817	4.750± 0.2887*	4.750± 0.2887	4.767± 0.4590	4.750± 0.2887	4.850± 0.4231	4.767± 0.4590	4.850± 0.4231
Running time of Rotarod	49.99± 7.789	52.43± 14.66	49.99± 7.789	43.83± 6.301	43.83± 6.301	49.02± 9.246	43.83± 6.301	51.44± 17.54	49.02± 9.246	51.44± 17.54
Ambulatory duration	211.78± 45.76544	189.875± 45.76544	211.78± 45.76544	104.4± 48.21860*	104.4± 48.21860	96.11667± 46.08351	104.4± 48.21860	78.61667± 42.35717	96.11667± 46.08351	78.61667± 42.35717
Distance in zone	3148± 1480	2031± 218.6	3148± 1480	784.4± 148.3*	784.4± 148.3	746.3± 467.5	784.4± 148.3	633.2± 960.3	746.3± 467.5	633.2± 960.3
Serum Cortisol	13.12±4.513	11.88±3.561	13.12±4.513	10.53± 2.869	10.53± 2.869	10.35± 1.948	10.53± 2.869	9.719± 2.925	10.35± 1.948	9.719± 2.925

*$p<0.05$, **$p<0.01$, ***$p<0.001$ compared to normal.

In the induction groups, results between groups were found to be statistically insignificant (Table 4). However, a noticeable mean difference was observed in ambulatory duration and distance travelled between the cisplatin group and the Atibala Kashaya-treated groups on the 45th day (Table 5). This discrepancy may be attributed to the higher standard deviation value.

The running time of the rotarod of the cisplatin group was [43.83±6.301] and that of that of the Atibala-treated groups D and E was [49.02±9.246] and [51.44±17.54], respectively.

The ambulatory duration of the cisplatin group [104.4±48.21860] and Atibala-treated groups D and E was [96.11667±46.08351] and [78.61667±42.35717], respectively.

The distance travelled in the actimeter of the cisplatin group [784.4±148.3] and *Atibala*-treated groups D and E was [746.3±467.5] and [633.2±960.3], respectively.

DISCUSSION

The primary objective of this study was to evaluate the Balya activity of Atibala by inducing muscle weakness through cisplatin administration. Cisplatin-based chemotherapy is associated with notable side effects, with muscle weakness and fatigue emerging as the most common adverse effects due to the depletion of skeletal muscle mass. The administration of Atibala Kashaya yielded significant improvements in the growth of muscle cells (Figure 1) and demonstrated its efficacy in alleviating the muscle weakness induced by cisplatin.

When comparing Group B (*Atibala*) to Group A (Normal), we found a statistically not significant but minimal increase in weight, thigh circumference, running time on the rotarod and actimeter distance travelled. Additionally, there was an observable improvement in the growth of muscle cells in Group B (Atibala Kashaya). These findings suggest that Atibala mula Kashaya has an effect on muscular structure, indicative of its Balya activity and health-promoting action.

Following the administration of cisplatin to groups C, D and E, a noticeable weight loss was observed (Figure 2), coupled with reduced food intake and histopathological changes in the muscle. This indicates the successful establishment of a cisplatin-induced muscle atrophy model. Our results demonstrated that animals treated with Atibala Kashaya in combination with cisplatin experienced less weight loss compared to those treated with cisplatin alone. These findings align with a study conducted by Wu CT *et al.* in 2021, [14] where skeletal muscle atrophy was observed on the 15th day in histopathology (Figure 1). The present study successfully elucidated a significant mean difference in weight and a considerable difference in mean thigh circumference.

Cisplatin toxicity initiates an increase in pro-inflammatory cytokines, primarily attributed to the generation of reactive oxygen species and oxidative stress. These cytokines subsequently

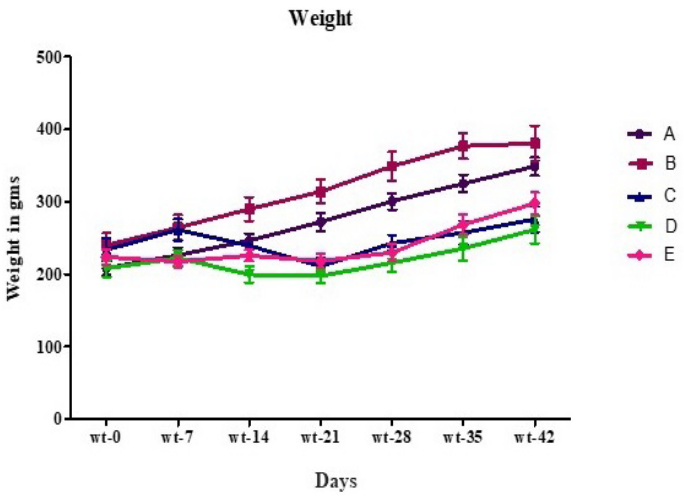

Figure 2: Effect of *Atibala Kashaya* on body weight (g).

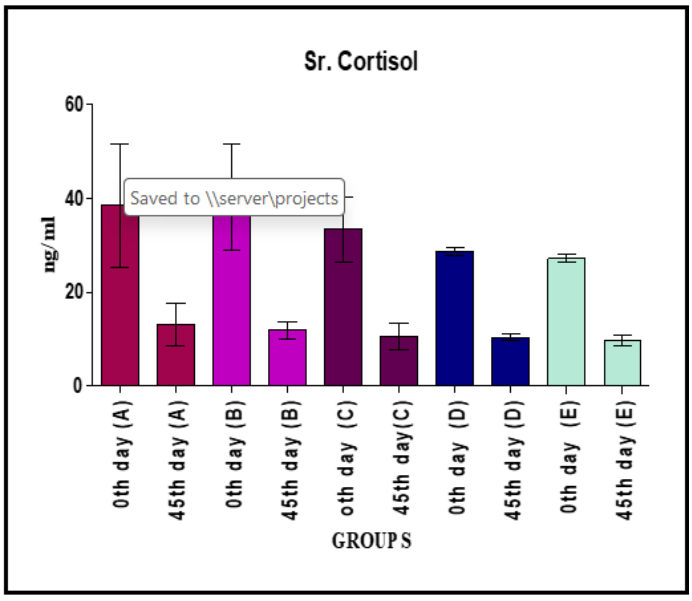

Figure 3: Effect of *Atibala Kashaya* on Serum Cortisol (ng/mL).

induce apoptosis and cellular damage. Reactive oxygen species inflict damage to the cell membrane through neutrophil activation and lipid peroxidation, culminating in muscle tissue atrophy.[15] Muscle cell culture studies indicate that cisplatin has the potential to activate genes associated with atrophy, stimulate proteasomal proteolysis and induce inflammation in muscle cells.[16]

Bala, or strength, is typically evaluated through vyayama shakti, which gauges the capability to perform exercises or work. Consequently, rotarod and actimeter models are employed to assess muscle strength based on activity. The most reliable way to screen for medications meant to increase muscle strength is the rotarod test. A previous study (Meena Manish *et al.*, 2019) observed the effectiveness of the Balya karma of Gilodya (Ceropegia bulbosa Roxb. var. bulbosa) against malnutrition, using Rotarod as one of the parameters.[8] In the present study, the rotarod is utilized to measure running time, serving as an indicator of muscle strength. Test groups (B, D and E) exhibited a higher mean difference before and after treatments compared to normal or disease control, although this difference was not statistically significant. Despite the notable difference, significance might not be evident in the study due to a high standard deviation. Similar trends were observed in the distance traveled in the actimeter.

One of the earliest hormonal alterations in cachexia is elevated cortisol production. In a murine cachexia model, serum cortisol concentrations increased concomitantly with weight loss. The mean difference in cortisol levels in test groups D and E is comparatively less when compared to the cisplatin and normal groups, suggesting that the test drug exhibits a cortisol-modulating effect (Figure 3). This adaptogenic activity of the plant is attributed to the presence of bioactive constituents such as flavonoids, fixed oils and alkaloids.[17] Larger sample size needed to overcome higher standard deviation.

FOXO-1, a member of the Foxo family of transcription factors, plays a pivotal role in the signalling pathways that lead to skeletal muscle atrophy. It becomes significantly more active in skeletal muscle during periods of energy deprivation, as seen in conditions such as cisplatin-induced anorexia cachexia. The compound beta-sitosterol demonstrates anti-catabolic effects on skeletal muscles by modulating the FoxO1/MAFbx pathway, which is responsible for muscle loss. This effect was substantiated through experiments conducted on C2C12 myotubes subjected to dexamethasone-induced muscle atrophy, as well as on mouse models. Consequently, beta-sitosterol exhibits promise as a potential treatment for age-related sarcopenia.[18] Atibala Kashaya has decelerated most of the pathophysiologic changes associated with cisplatin-induced cachexia. This effect may be attributed to the presence of herbal actives like beta-sitosterol.

Limitations

Larger group studies may be needed to find out whether this lead is useful. The samples for assessing serum cortisol levels were collected during the afternoon; however, it wasn't possible to collect samples during the late evening, which is when the rats' highest activity period commences (past 7 p.m.). Additionally, this investigation specifically focused on male rats, omitting the inclusion of female rats.

CONCLUSION

The results of the previously described study clearly show that *Atibala Kashaya* treatment was effective in reducing muscle weakness. Consequently, the use of Atibala Kashaya may be recommended as an adjunct therapy to mitigate the complications associated with chemotherapy. Further investigations with larger sample sizes and robust clinical trials are suggested to enhance the validation of these observations.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

CPCSEA: Committee for the Purpose of Control and Supervision of Experiments on Animals; **AYUSH:** Ayurveda, Yoga, Unani, Siddha and Homeo (Ministry under Government of India; **ASU DTL:** Ayurveda, Siddha and Unani Drug Testing Laboratory; **ICMR-NITM:** Indian Council for Medical Research National Institute of Traditional Medicine; **SOP:** Standard Operative Procedure; **mL:** Milliliter; **cm:** Centimetre; **ng:** Nanogram; **S.D.:** Standard Deviation; **FOXO-1:** Forkhead box protein O1; **MAFbx:** Muscle Atrophy F-box; **C2C12:** An immortalized mouse myoblast cell line.

SUMMARY

Muscle weakness and atrophy are found in different conditions like old age, post-anticancer treatment, immune mediated diseases etc., affecting many people and many wish to improve muscle bulk and strength. Herbs used in traditional medicine to improve muscle bulk and strength like *Sida cordifolia* root decoction administered orally, is evaluated in the present study in experimental animal model. Study design includes normal animals to study muscle improvement and also model for cisplatin induced muscle cachexia. Beyond muscle bulk, functionality was assessed through rotarod and actimeter. serum cortisol and histopathology of calf muscle was studied. Study showed nonsignificant improvement in above parameters in the test groups when compared to control group, but showed leads that test drugs might have a beneficial role, which can be seen in histopathology study. Further evaluation might be helpful in screening herbs which can benefit the people suffering from cachexia and might provide scientific validation of traditional medical system.

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