



ORIGINAL RESEARCH ARTICLES

Effect of Boswellia Adjuvant Induced Rheumatoid Arthritis in Experimental Animals

Omnia Magdy Mohammed Hendawy Hendawy*¹ and Della Grace Thomas Parambi²**Abstract**

Arthritis is the most common systemic connective tissue disease. About 1% of the world's population is affected by RA; women are three times more often than men. Onset is most frequent between the ages of 40 and 50 years, but people of any age can be affected. Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disorder that may affect many tissues and organs, but principally attacks flexible joints. Although the cause of rheumatoid arthritis is unknown, autoimmunity plays an important role in both its chronicity and progression.

The new trend of medical treatment of rheumatoid arthritis seeks for new drugs with more efficacy and less side effects. Since tumor necrosis factor alpha (TNF- α) as well as other cytokines act as key players in the development of arthritis.

Studies in the United States and Europe have shown that their use is less common in clinical settings, but has become increasingly more in recent years as scientific evidence about the effectiveness of herbal medicine has become more widely available. The present work investigates the effect of Boswellia on Adjuvant induced RA in Experimental Animals.

Keywords: Rheumatoid Arthritis; Complete Freund's Adjuvant; Boswellia

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disorder that attacks flexible joints and also may affect many tissues and organs. The process involves an inflammatory response of the capsule around the joints secondary to swelling of synovial cells, excess synovial fluid and the development of pannus in the synovium. This will lead to destruction of articular cartilage and ankylosis of the joints. Rheumatoid Arthritis affect multiple other organs of the body so it is referred as a systemic illness and is sometimes called rheumatoid disease. Rheumatoid arthritis itself is not a fatal disease. However, it can be associated with many complications and treatment-related side effects that can contribute to premature death [1]. Since the traditional anti-rheumatoid drugs causes numerous adverse effects, we seek for new treatment with more efficacy and less side effects.

Plants have the ability to synthesize a wide variety of chemical compounds that are used to perform important biological

functions, and to defend against attack from predators such as insects, fungi and herbivorous mammals. Chemical compounds in plants mediate their effects on the human body through processes identical to those already well understood for the chemical compounds in conventional drugs; thus herbal medicines do not differ greatly from conventional drugs in terms of how they work. This enables herbal medicines to be as effective as conventional medicines, but also gives them the same potential to cause harmful side effects [2]. The use of herbs to treat disease is almost universal among non-industrialized societies, and is often more affordable than purchasing expensive modern pharmaceuticals. The World Health Organization (WHO) estimates that 80 percent of the population of some Asian and African countries presently use herbal medicine for some aspect of primary health care. [3]. The Earth biological communities containing a colossal mass of plants and creatures whereupon all other living structures are straight forwardly or in a roundabout way needy, Man's aggre-

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gate reliance on it for his reality has been of imperative significance. The necessities of life sustenance, apparel, protect, agribusiness, pharmaceutical, and so forth are provided in incredible part by plants. To the extent the ethno botany is concerned it merits considering. An appropriate documentation of crude learning is basic in light of the fact that the ethnic bunches have gained it by long understanding and steady touch with the timberland. They try not to try and have any composed records yet give the learning orally to straightaway age. Be that as it may, the new age is slightest inspired by this information? Be that as it may, the majority of the ethno botanical thinks about seem to have been confined among the tribals or urban individuals for recording their insight about plant riches what's more, look for new assets of consumable plants, home grown medications and different parts of plants. The other three angles and the urban populaces have for the most part been cleared out. Presently a day the term ethno botany applies to add up to between connection between individuals and plants. Also financial botanists and pharmacologists can use the documentation of ethno botany/ethno medicine implies it is the main wellspring of interrelationship amongst humankind and plants. [4]. Boswellia acids, which are sweet-smelling, multi-ringed natural mixes found in Indian frankincense, add to frankincense's hostile to rheumatic properties. It is known to have originated in the dry areas of India, Africa, & the Mediterranean. Boswellia is a true super-food shown to have remarkable healing and anti-inflammatory properties that are just now being discovered. Boswellia acids restrain 5-lipoxygenase, a compound which empowers the arrangement of leukotrienes, aggravates that reason irritation in different kinds of diseases including joint inflammation, asthma, and so on. The gum oleoresin comprises of terpenoids, fundamental oils and gum. The dynamic constituents in boswellia are terpenoid it contains Boswellia acids. The concentrates are containing 37.5– 65% Boswellia acids. Plant is utilized in the calming, hostile to malignancy action and against joint. The generation of Boswellia acids in plants has a place with the class of Boswellia. *B*-Boswellia corrosive has frightful in apoptosis of growth cells [5]. Boswelliaserrate has additionally gone about as a hostile to joint, pain relieving and calming. 3-O-Acetyl-11-keto-beta-boswellic corrosive (AKBA) is the dynamic compound of Boswellia remove. Boswellia removes which is going about as a hostile to joint and calming properties. Boswellia acids are pentacyclic triterpenic acids that dynamic parts of the plants have calming and anticancer properties which situated at the periodontal gum. Boswellia acids are as of now helpful for treating Crohn illness, bronchial asthma and joint pain. [6].

Many studies have shown that Boswellia is just as effective as non-steroidal anti-inflammatory drugs (NSAID's), which are

the most commonly used treatment for inflammation and chronic pain. NSAID's work by inhibiting the inflammatory promoting cyclooxygenase-2 (COX-2) enzymes. Unfortunately, these drugs also inhibit COX-1, which is essential for a healthy stomach lining. This is why these medications cause stomach bleeding. They also deplete the body of anti-oxidant trace minerals like selenium and zinc as well as key vitamins needed to naturally reduce inflammation. [7]. Boswellia works to reduce inflammation through a different mechanism. It acts to modulate the pro-inflammatory enzyme 5-lipoxygenase (5-LOX). 5-LOX is the first enzyme released in the cytokine metabolic pathway. This pathway creates leukotrienes, which are strong inflammatory substances thought to influence many disease processes including cancer, rheumatoid arthritis, & asthma. The immune modulation reduces inflammatory chemicals and symptoms of inflammation. These boswellic acids also reduce another inflammatory enzyme called human leukocyte elastase (HLE). HLE and 5-LOX are both classically elevated in inflammatory conditions and diseases. Boswellia is the only known substance to reduce both HLE and 5-LOX. Boswellia also reduces the expression of the cytokine tumor necrosis factor alpha (TNF- α). In fact, it is thought that boswellia's success in relieving symptoms of arthritis is due to its ability to inhibit the breakdown of connective tissue caused by TNF- α induced expression of matrix metalloproteinase enzymes. [8].

Material and Methods

Animals arrangement and RA Induction

Male Lewis rats (Harlan Sprague Dawley, Indianapolis, IN), 5-month and a half old, were kept under controlled natural conditions (22 ± 0.5 °C relative stickiness 40– 60%, 7 a.m. to 7 p.m. substitute light– dull cycles, nourishment and water not obligatory). The animals were obtained 1 week before the trial and permitted to adapt. They were housed in confines in which the floor was secured with sawdust to limit the likelihood of agonizing contact with a hard surface. The animals' conventions were affirmed by the Institutional Animal Care and USA Committee (IACUC) of the University Of Maryland School Of Medicine, and the moral rules for the treatment of creatures of the International Association for the Study of Pain were followed in all analyses. [9]. RA was instigated in the Lewis rats by infusing 200 [10].

Joint pain evaluations

Rats were surveyed day by day for indications of joint pain between days 7 and 25 post-Complete Freund's Adjuvant utilizing a standard joint scoring framework. The maximal ligament score

per rodent was set at 16 (greatest of 4 focuses \times 4 paws). Every one of the four paws were inspected and evaluated for seriousness and loci of erythema, swelling and induration utilizing a 5-point scale: 0 = no indications of illness; 1 = signs including the lower leg/wrist; 2 = signs including the lower leg in addition to tarsals (proximal piece of the rear paw) or potentially wrist in addition to carpals of the forepaw; 3 = signs stretching out to the metatarsals or metacarpals; and 4 = extreme signs including the whole rear or fore paw. Paw volume was estimated each other day between days 16 and 24 with a paleothermometer (IITC Inc., Woodland Slopes, CA), which comprises of two vertical, interconnected, water-filled Perspex cells. The paw to be estimated is plunged into the bigger cell to the lower leg line causing the water level in the littler cell, which contains a transducer, to rise. The transducer changes over recognized paw volume into milliliters, at that point registers the correct volume electronically on a screen. Add up to paw volume, or the entirety of the four paws, was ascertained. To maintain a strategic distance from potential predisposition, examiners playing out all evaluations or estimations were blinded to treatment bunch assignments [11].

Home grown planning and extraction

Natural Boswallia Acid gum tar was acquired from the Tong Ren Tang pharmaceutical organization (Beijing, China) and the tar was distinguished by the most recent Pharmacopeia of the People's Republic of China (2000). It was ground into powder (~80 work) and prepared at room temperature with 70% watery CH₃2CO to totally remove both non-polar also, polar parts. Dissipation temperatures were kept underneath 55 °C to limit the conceivable breakdown of thermolabile exacerbates that might be available in extricates. This underlying unrefined concentrate was thought under decreased weight, and the dried buildup was coded and weighed for the investigation. The last concentrate was 40% the heaviness of the crude sap. The nature of the concentrate was observed utilizing elite fluid chromatography (HPLC). The BC separate utilized as a part of this examination was from a solitary [12, 13].

Natural organization

Rats were haphazardly partitioned into a BC treatment gathering (n = 8) and a vehicle control gathering (n = 8). The dose of BC removes utilized as a part of this investigation was 0.90 g/kg every day, which is the ideal measurements found out in past examination [14]. This is equivalent to using 100 g of raw BC resin in a human decoction (the rate of hot aqueous extract being 10%) as calculated by the method described in. Between days 16 and 25 post- CFA injection, the rats received either BC or vehicle once a day for 10 consecutive days. Each dose of BC extract was dissolved

in 2 ml of distilled water and sesame oil (2:1) and administered intranasally (e.g.), using a 5 ml syringe with a 4 cm long gavage needle. Animals in the vehicle control group received daily e.g. doses of 2 ml distilled water and sesame oil (2:1).

Local tissue collection and ELISA

For cytokine assay, the local tissue was collected from the BC treatment and vehicle control animals at day 25 posca following the arthritis assessments. Local tissue was also collected from a group of non-inflamed, normal animals treated with vehicle that served as a background control. After the rats were deeply anesthetized with sodium pentobarbital (80 mg/kg, imp.), soft tissue (1.0 g) was collected from the ankle, immediately placed on ice, and then homogenized using an ultrasonic processor (Cole-Parmer Instruments, Vernon Hills, IL). Tissue supernatant samples were frozen for storage (-80 °C) immediately after collection to prevent cytokine degradation. IL-1 and TNF- levels were measured using enzyme linked immunosorbent assay (ELISA) kits according to the procedure recommended by the manufacturer (BioSource International Inc., Camarillo, CA). In brief, IL-1 levels were measured by pipetting 50 [15].

Toxicity/adverse effects assessment

Standard pharmacological categories of toxic and adverse behavioral reactions were used, following the methods described by. Animals were closely monitored for unusual behavioral changes and such symptoms as obvious temperature change (rectal temperature was taken with a digital thermometer before each BC or vehicle administration), diarrhea, weight loss (rats were weighed every other day), fur discoloration, lethargy, irritation and convulsion during the 10 days of treatment. After the observation period, all animals was euthanized and a gross necropsy was performed. All observations were performed by investigators who were blinded to treatment group assignments [16].

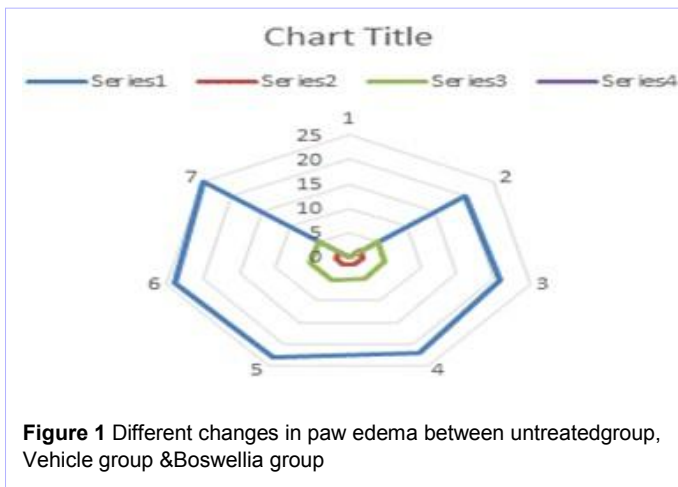
Statistical analysis

The number of animals used in each specific test was estimated via a power analysis based either on our own preliminary data or on published results employing similar experimental procedures and physiologic parameters. For arthritic score and edema assessments, one-way repeated measure ANOVA was used for statistical comparison between the two groups; for cytokine testing, one-way ANOVA was used for statistical comparison. All post hoc comparisons were conducted using the Dennett test. P < 0.05 was considered significant in all cases.

Results

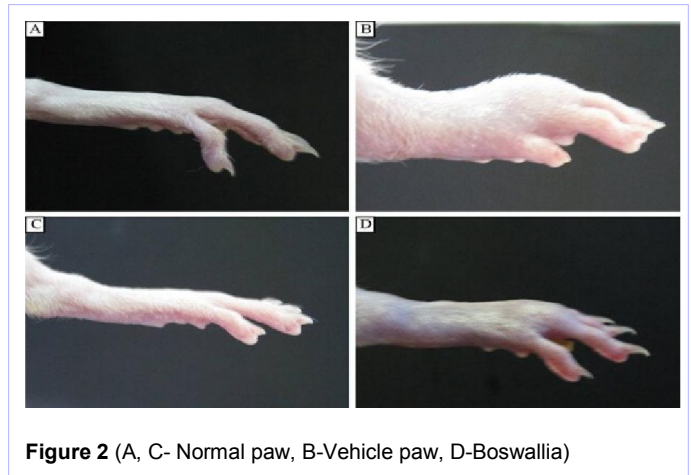
BC decreases arthritic score and paw edema

The rats gradually developed multiple-joint RA beginning on day 8 after CFA was injected at the base of the tail. The manifestations peaked between days 18 and 20. There were no significant differences in arthritic score or edema between the two groups before BC or vehicle administration on day 16 ($p > 0.05$). BC extracts at daily 0.90 g/kg significantly suppressed arthritic scores compared to vehicle control between days 20 and 25 post-CFA. (On day 20: 2.09 ± 0.55 versus 4.97 ± 0.82 ; on day 21: 1.90 ± 0.51 , versus 5.03 ± 0.76 ; on day 22: 1.81 ± 0.52 versus 5.03 ± 0.77 ; on day 23: 1.75 ± 0.50 versus 5.22 ± 0.76 ; on day 24: 1.62 ± 0.46 versus 5.19 ± 0.73 ; on day 25: 1.62 ± 0.52 versus 5.09 ± 0.71 , individually. $F = 15.64$, $p < 0.001$). Paw edema was lessened fundamentally contrasted with control on days 18, 20 what's more, 22. (On day 18: 5.25 ± 0.23 ml versus 6.05 ± 0.44 ml; on day 20: 4.87 ± 0.23 ml versus 5.98 ± 0.43 ml; on day 22: 4.81 ± 0.11 versus 5.93 ± 0.46 ml, individually. $F = 5.21$, $p < 0.001$) (Figure 1) (Figure 2).

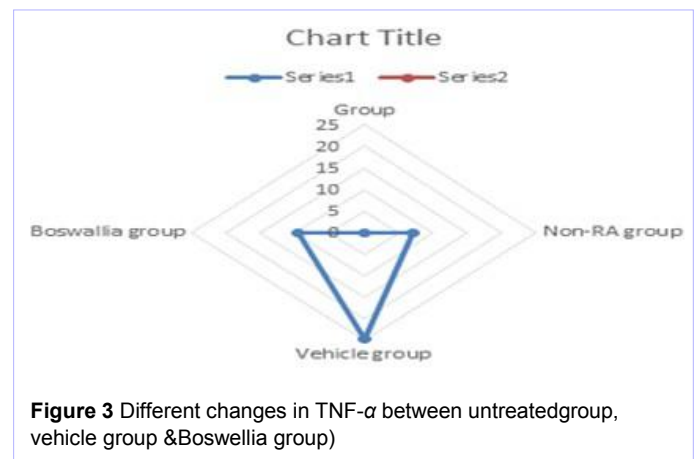


BC diminishes cytokine levels in nearby ligament tissue

On day 25 post-CFA infusion, there were noteworthy contrasts in neighborhood tissue TNF- levels among BC treatment (9.56 ± 2.84 pg./mg protein), vehicle control (24.78 ± 4.18 pg./mg protein) and non-RA typical creature (7.27 ± 1.80 pg./mg protein) gatherings ($F = 7.87$, $p = 0.005$). Levels in the vehicle control RA gather were around three times higher than that of the typical creature gathering ($q = 3.84$, $p < 0.01$). The BC extricate altogether smothered neighborhood TNF- contrasted with the RA control gathering ($q = 3.01$, $p < 0.05$; Comparative outcomes were found in the neighborhood tissue IL-1 test ($F = 7.30$, $p = 0.007$) (Figure 3). The concentrate altogether stifled IL-1 levels

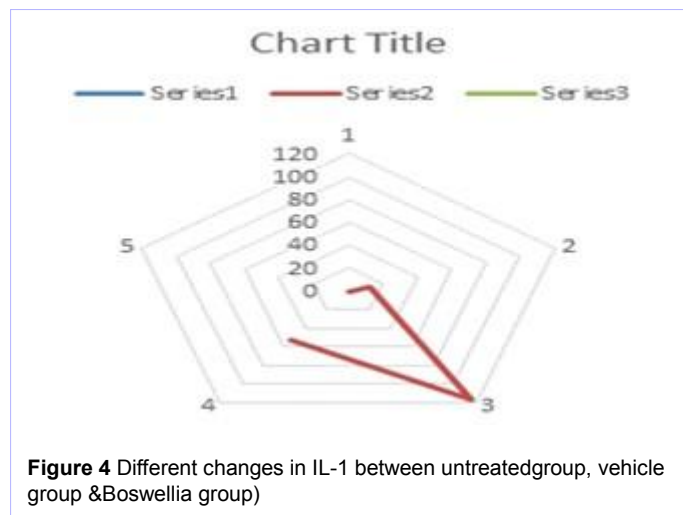


(53.39 ± 7.69 pg./mg protein) contrasted with vehicle control (117.29 ± 25.58 pg./mg protein; $q = 2.39$, $p < 0.05$, while IL-1 levels were low in non-RA ordinary rats (12.45 ± 2.90 , $q = 4.08$, $p < 0.05$) (Figure 4) contrasted with control.



Lethality or unfriendly impacts of the BC extricate

Amid the 10 days of day by day e.g. organization, no huge behavioral changes or evident manifestations with the exception of signs related with the CFA-incited RA were seen in either vehicle control or the BC treatment gatherings. In any case, mellow hide staining was seen in a few creatures (two of eight) treated with 0.90 g/kg BC. There was no distinction in body weight between the treatment and vehicle control rats previously BC organization on day 16 post-CFA (206.13 ± 9.93 g versus 202.25 ± 4.82 g; $p > 0.05$). On day 25, treatment gathering body weight was essentially higher contrasted with that of control ($224.63 \pm g$ versus 188.88 ± 3.92 g, $p < 0.05$), recommending that the creatures treated with BC were more outlandish to get thinner from RA. In the gross necropsy considers, no harm to organs



or tissues, including stomach ulcers or then again draining foci, was found in any creature.

Discussion

The present investigation showed that the Chinese herb Ruxiang (BC) at a day by day measurement of 0.90 g/kg fundamentally weakened adjuvant-actuated poly arthritis as appeared by the abatement of both joint score and paw edema volume. The adjustments in ligament score and paw edema volume were decidedly related. These discoveries are reliable with the consequences of past investigations, including our own that demonstrated the mitigating, pain relieving and against hyperalgesic impacts of BC on various creature models [17]. CFA-actuated optional irritation copies sub-intense RA. (10) Since RA is portrayed by over the top immunologic movement in the synovium, the counter poly arthritis impact of BC might be accomplished by the potential immunomodulatory properties of BC. The primary concoction constituents of the BC extricate are boswellic acids [18]. It has been accounted for that boswellic acids specifically diminish the development of leukotriene LTB₄, a strong chemo attractant also, activator of the two granulocytes and macrophages and decrease the penetration of leukocytes into an aggravation site. It is notable that leukocytes create expert fiery cytokines, for example, TNF-, IL-1 and IL-6, which assume essential parts in both RA in people and RA in rats. Our information show that the BC extricate fundamentally diminishes the neighborhood tissue pro inflammatory cytokines TNF- and IL-1 that were incited by CFA aggravation. Past investigations have demonstrated that the against joint impacts of a few other Chinese home-grown items may likewise include the neighborhood tissue cytokine pathway [19]. For instance, PG201, an ethanol concentrates of a natural recipe, fundamentally hindered the

generation of the professional provocative middle people TNF- and IL-1 in nearby joint tissue and smothered the movement of collagen-initiated joint pain in mice [20]. Taking this information together, we reason that the antiarthritic impact of BC and other hostile to ligament Chinese herbs may come about because of the concealment of IL-1 and TNF- and the interference of the cytokine pathway amid the procedure of neighborhood tissue aggravation. As of late, Chinese herbs have turned into a well-known correlative treatment among patients, and various examines show their utility and investigate their conceivable systems. This across the board use has raised worries in the medicinal group over the well being and conceivable reactions of herbs. Amid the 10-day rehashed measurements use of BC, we watched no critical antagonistic impacts. Be that as it may, the high measurements of BC utilized as a part of this investigation may clarify the hide staining saw in a portion of the creatures, which may connote the potential for antagonistic impacts. Regardless, before BC is subjected to a clinical trial, a creature poisonous quality investigation equal to the length of the clinical trial, yet no less than 2 weeks in length, must be performed (Nourishment and Medication Organization, 2004). It is important that the successful measurement (0.9 g/kg) we utilized as a part of the present investigation is identical to 100 g BC crude sap, or on the other hand 10 times the sum (10 g) more often than not added to homegrown equations recommended for human utilize. This recommends, to accomplish a remedial impact, a substantially higher dose is required when an individual herb is utilized alone than when it is utilized as a part of a home-grown equation. As indicated by Chinese home-grown hypothesis, connections among the distinctive herbs in an equation may apply an added substance or synergistic impacts that amplify the restorative impacts and kill the toxicities or reactions of the individual constituents [21]. Be that as it may, further examination of the security, adequacy and instruments of BC and its cooperation's with different herbs in established Chinese home-grown recipes is justified.

Conclusions

Home grown prescriptions are prominent as solutions for illnesses by tremendous greater part of total populace. Therapeutic plants are a wellspring of extraordinary monetary esteem everywhere throughout the world. Nature has presented on us an exceptionally rich plant riches and an extensive number of various sorts of plants develop in various parts of the nation. There is extensive confirmation that plant separates can possibly be produced into operators that can be utilized as deterrent or treatment treatments for oral illnesses. In this audit, we have chosen some therapeutic plants as of late that feature a portion of the fun-

damental advances accomplished in the distinguishing proof of plants with hostile to ligament movement. So that *Boswellia* extract showed a powerful anti-rheumatoid activity with less toxic adverse effects.

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