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DRUG INTERACTION BETWEEN MELOXICAM AND MAJOON SURANJAN (A POLYHERBAL UNANI FORMULATION)

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Abstract:

Majoon Suranjan (MS) is a polyherbal formulation used in Unani system of medicine for the treatment of rheumatoid arthritis (RA). It is prescribed by unani practitioners and there is no objectionon the concomitant use of this formulation along with conventional NSAIDs. Present study deals with the pharmacodynamics interaction of conventional NSAID with majon suranjan. Interaction was studied by the influence on the anti-inflammatory activity of the standard drug in turpentine oil induced paw edema, and anti-arthritic activity in formaldehyde and complete fruend's adjuvant induced arthritis. In all these three methods meloxicam was used as the standard conventional NSAID . 3 Groups of male whistar rats (n=6) were used in this study. Group I received vehicle, Group II received meloxicam and III received combination use of meloxicam and majoon suranjan. In turpentine oil induced rat paw edema anti- inflammatory activity of group III is superior to Group II. Anti arthritic activity of group III is less when compared to Group II in formaldehyde and adjuvant induced arthritis models. Data of these three methods are analysed by annova and dunnetts multiple comparison at $p<0.05$ in turpentine oil indued rat paw edema and $p<0.01$ in formaldehyde and adjuvant induced arthritis models. Results suggest that there exist an interaction between conventional NSAIDs and polyherbal formulation whether it may be positive or negative type. These results suggests that based on the pathology of disease interaction of NSAIDs with polyherbal formulation differs. In present study anti inflammatory acivity of drug increased while anti arthritic activity decreased.

Keywords : Majoon Suranjan, meloxicam, Turpentine, Formaldehyde, NSAIDs, adjuvant induced arthritis.

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INTRODUCTION

Rheumatoid arthritis is the most common systemic inflammatory disease characterized by symmetrical joint involvement. Extra articular involvement, including rheumatoid nodules, vasculitis, eye inflammation, neurologic dysfunction, cardiopulmonary disease, lymphadenopathy, and splenomegaly, can be manifestations of the disease[1].

Rheumatoid arthritis is estimated to have a prevalence of 1% to 2% and does not have any racial predilections. It can occur at any age, with increasing prevalence up to the seventh decade of life. The disease is three times more common in women. In people ages 15 to 45 years, women predominate by a ratio of 6:1; the sex ratio is approximately equal among patients in the first decade of life and in those older than age 60 years [1].

Epidemiologic data suggest that a genetic predisposition and exposure to unknown environmental factors may be necessary for expression of the disease. The major histocompatibility complex molecules, located on T lymphocytes, appear to have an important role in most patients with rheumatoid arthritis. These molecules can be characterized using human lymphocyte antigen (HLA) typing. A majority of patients with rheumatoid arthritis have HLA-DR4, HLADR1, or both antigens in the major histocompatibility complex region. Patients with HLA-DR4 antigen are 3.5 times more likely to develop rheumatoid arthritis than those patients who have other HLA-DR antigens.1 Although the major histocompatibility complex region is important, it is not the sole determinant, because patients can have the disease without these HLA types. Rheumatoid arthritis is six times more common among dizygotic twins and nontwin children of parents with rheumatoid factor-positive, erosive rheumatoid arthritis when compared with children whose parents do not have the disease. If one of a pair of monozygotic twins is affected, the other twin has a 30 times greater risk of developing the disease [2,3].

The current therapies used to treat RA include non steroidal anti inflammatory drugs (NSAIDs), used for the management of pain and inflammation; disease-modifying antirheumatic drugs (DMARDs), used as first-line therapy for all newly diagnosed cases of RA; and biological-response modifiers, targeted agents that selectively inhibit specific molecules of the immune system. Glucocorticoids and other antirheumatic drugs are also used to treat RA. DMARDs include methotrexate, hydroxychloroquine, sulfasalazine, and leflunomide. NSAIDs and glucocorticoids are effective in controlling the pain, inflammation, and stiffness related to RA. Unlike NSAIDs, they slow clinical and radiographic progression of RA. The biological-response modifiers include infliximab, etanercept, and adalimumab (inhibitors of tumor necrosis factor [TNF]-α); anakinra, a recombinant inhibitor of interleukin-1; abatacept, the first costimulation blocker; and rituximab, a chimeric anti-CD20 monoclonal antibody. Investigational therapies for RA include anti-interleukin-6-receptor monoclonal antibodies, new TNF-α inhibitors (including one for oral administration), and antibodies against proteins critical for B-cell function and survival. Data accumulated in the past decade favor early aggressive therapy for patients suspected of having RA, including early referral to a rheumatologist, new diagnostic techniques, and aggressive therapy with DMARDs, glucocorticoids, and biological agents [4]**.**

Many patients look for complementary and alternative medicine (CAM) options in coping with this debilitating disease. Research has indicated that people suffering from chronic pain, as in RA, and those dissatisfied with current treatment are very likely to seek alternative treatments, and an estimated 60–90% of persons with arthritis use CAM. Among the most widely used treatments are chiropractic and herbal therapies. This growing interest in alternative medical practices clearly indicates the need for more thorough investigation into the safety and efficacy of CAM. These CAM's include Borage seed oil, Boragoofficinalis, Evening primrose oil, Oenotherablennis, Blackcurrant seed oil, Ribesnigrum, Capsaicin, Curcumin (diferuloyl methane), Feverfew (Tanacetumparthenium), Flaxseed oil, H15 (extract of Boswelliaserrata, olibanum), RA-1 (standardized Ayurvedic formulation), Reumalex, which is a herbal mixture containing 100 mg Pulv White Willow Bark BHP, 40 mg Pulv guaiacum resin BHP, 35 mg Pulv Black Cohosh BHP, 25 mg Pulv Ext Sarsaparilla 4:1 and 17 mg Pulv Ext Poplar Bark 7:1[5].

CAM is defined as a 'diagnosis, treatment and/or prevention which complements mainstream medicine by contributing to a common whole, by satisfying a demand not met by orthodoxy orby diversifying the conceptual frameworks of medicine'[6].

In India, alternative systems such as Ayurveda, homoeopathy, Siddha and Unani medicine are supported by the Government of India [7].

CAM practices and modern, allopathic medicine run parallel to each other and may cater to the rural and urban populations, respectively, though not mutually exclusively. CAM therapies cater to a large proportion of the Indian population. A stance of outright rejection adopted by many physicians often results in patients withholding all information about

CAM use from the treating physician. This is a source of major concern because of the high probability of drug interaction, especially in the case of orally administered drugs [8,9,10].

Although most herbal medical practitioners claim safety with the concomitant use of both herbal and orthodox medicines, the possibility of drug interaction cannot be ruled out. The larger proportion of these patients do not inform their health care givers as to the use of herbs with allopathic medicines, and most physicians and pharmacists do not enquire about herb use of their patients, probably believing that there is no such need. Studies have shown that consulting with physicians does not prevent patients from coadministering prescription medicines and herbal medicines [11,12,13]. More than one-third of the ambulatory hypertensive patients interviewed in a Nigerian hospital were found to be using herbal medicine [14]. Although almost all the plants used by the respondents have proven ethnopharmacological and folkloric uses, this practice could be potentially harmful as far as the health of the individual is concerned.

Quite a number of physicians and pharmacists believe that there may be drug–herb interactions,but not much effort is made to investigate patients' herb use. This oversight might have contributed to some of the incidencesof side effects experienced as a result of herb use by some patients, which could have been prevented if they had been advised appropriately e.g. gingko interacts with aspirin with the potential of increased risk of bleeding, ginseng may interact (unpredictable) with warfarin hence the concomitant use may lead to a risk of prolonged bleeding, and St. John's wort may decrease theophylline's plasma concentration, thereby reducing its therapeutic effect [15]**.**

Patients suffering from rheumatoid arthritis are using the different polyherbal formulations along with the conventional NSAIDS. Efficacy of these polyherbal formulations are reported but their combination with NSAIDS will lead to the drug-herb interaction. Many unani practitioners argue that such polyherbal formulations do not interact with regular allopathic medicine. Hence the present study is designed to investigate the interactions between the regularly prescribed NSAID (meloxicam) and unani polyherbal formulation (Majoon suranjan).

MATERIALS AND METHODS

Drugs: The polyherbal formulation Majoon suranjan was obtained from Hamdard laboratories, New Delhi. Meloxicam was obtained as pure drug from Sun Pharmaceutical Industrie Ltd, Mumbai, India. And Meloxicam from Cipla Pharmaceuticals Ltd, Hyderabad, India.

Chemicals:

Turpentine oil, formaldehyde and complete fruend's adjuvant (CFA) were purchased from Sigma-Aldrich Pvt Ltd, Hyderabad, India. Mercury was obtained from vaagdevi college laboratory.

Experimental Animals:

Healthy Wister albino rats, weighing 200-220g, and healthy male albino rabbits, weighing 1.2-1.5kg were procured from the TeenaBiolabs Pvt. Ltd. (Reg, no. 177/99 CPCSEA), Hyderabad, Andhra Pradesh. Animals were housed at CPCSEA approved animal house of VaagdeviInstitute of Pharmaceutical Sciences, (1533/PO/a/11/CPCSEA) Warangal. The animals were kept under standard laboratory condition (12 hr light and 12 hr dark cycle) and had free access to commercial pellet diet (Vyas labs Ltd, Hyederabad, India) with water *ad libitum.* The animal house temperature was maintained at 25 ± 2^0C with relative humidity at (50 ±15%). The study was approved by the Institutional Animal Ethical Committee of Vaagdevi Institute Of Pharmaceutical Sciences, dated (14/03/2012). Ethical norms were strictly followed during all experimental procedure.

Exprimntal Design:

Group I –Control (Vehicle)
Group II – Standard (Meloxicam)
Group III – Test (Meloxicam+Majoon suranjan)

Turpentine Induced Paw Edema [16,17]:

Three groups of male wistar rats (n=6) were fasted overnight. Baseline paw volume was measured using Plethysmometer. Group I received vehicle (2mg/kg), group II received meloxicam(1mg/kg), group III received majoonsuranjan(1800mg/kg)+meloxiam (10mg/kg).Thirty minutes after administration of the vehicle/drug, oedema was induced by administration of 0.05 ml of turpentine oil into the sub plantar surface of the left hind paw of the animal. Increase in volume of the injected paw was measured at 1, 3 and 6 h post turpentine oil administration.

In turpentine induced paw edema increase in paw edema was calculated from the final paw volume at 1st, 3rd, and 6th hour of turpentine injection and baseline paw volume before turpentine injection.

Increase in paw edema (ml)
= Final paw volume (ml)at 1, 3, 6th hour of turpen

Formaldehyde Induced Arthritis [18,19]:

Three groups of male wistar rats (n=6) were used in the study. Drugs/vehicle was administered for duration of 10 days.Baseline recording of the joint diameter was made by using a micrometer screw gauge. Group I received vehicle (2mg/kg), Group II received meloxicam(1mg/kg), Group III received majun-e-suranjan(1800mg/kg)+meloxiam (10mg/kg). Drugs/vehicle was administered for duration of 10 days. Thirty minutes after administration of vehicle/drugs, arthritis was induced by subplantar administration of 0.1 ml formaldehyde (2% v/v) into the left hind paw of all the animals on days 1 and 3 as previously reported. Thirty minutes after administration of the respective vehicle/drug treatment, increase in the joint diameter of the injected paw was measured on days 8, 9 and 10.

Increase in joint diameter of control, meloxicam treated and meloxicam+majoonsuranjan treated group was calculated by baseline joint diameter and final joint diameter after injection of formaldehyde on day 8, 9,and 10.

$$\text{Increase in joint diameter (mm)} = \text{Final joint diameter (mm) on } day\ 8th,\ 9th \text{ and } 10th - baseline\ joint\ diameter$$

Adjuvant Induced Arthritis [20,21]:

Three groups of male wistar rats (n=6) were used. Baseline recording of the joint diameter was made by using a micrometer screw gauge. Group I received vehicle (2mg/kg), group II received meloxicam(1mg/kg), Group III received majun-e-suranjan(1800mg/kg)+meloxiam (10mg/kg). Thirty minutes after administration of the vehicle/drug, arthritis was induced by subplantar administration of 0.1 ml of CFA (0.05% w/v *Mycobacterium butyricum*in mineral oil) into the left hind paw of all rats. This was designated as day 0. After immunization with CFA, all the groups were maintained on vehicle/drug treatment for 20 days. Thirty minutes after vehicle/drug administration, joint diameter of the injected paw was again measured on days 7, 14 and 21.

Increase in joint diameter (mm) was calculated by baseline joint diameter and final joint diameter of all three groups on day 7, 14 and 21 of adjuvant injection.

$$\text{Increase in joint diameter (mm)} = \text{Final joint diameter (mm) on } day\ 7, 14, \text{ and } 21 -$$

Statistical analysis:

The results were expressed as mean ± S.E.M. The results were analyzed statistically by two way ANOVA, followed by Turkey's multiple comparison test. Values $p < 0.05$ were considered Significant.

RESULTS AND DISCUSSION

Turpentine Induced Paw Edema:

The increase in paw edema is significantly low in both Group II and Group III when compared to control at 1st, 3rd , and 6th hour of measurement. When the Group II is compared with that of Group III in multiple comparisons the increase in paw dema of Group III at 6th hour was found to be significantly low of 0.163±0.086 at $p<0.05$ compared to Group II .

Table 1: Turpentine Induced Paw Edema In Rats

Groups	Increase in paw edema in ml of mercury		
	1st hour	3rd hour	6th hour
Control (Vehicle)	0.685±0.097	0.868±0.122	0.881±0.160
Standard (Meloxicam)	0.195±0.088	0.243±0.058	0.293±0.038
Test (Meloxicam+ Majoon suranjan)	0.241±0.127Ns	0.263±0.069Ns	0.163±0.086*

** Significantly different from standard at p<0.05*

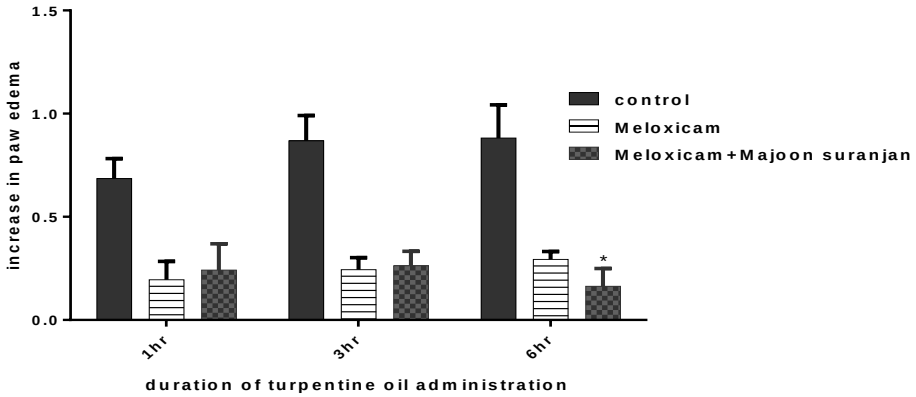

Fig 1: Turpentine Induced Paw Edema In Rats

Formaldehyde Induced Arthritis:

The increase in joint diameter of Group III and Group II was found to be significantly low on 8th, 9th and 10th day when compared to control (Group I). But the increase in joint diameter of Group III on 8th , 9th and 10th day is more when compared to Group II and it is significant at $p<0.05$.

Table 2: Formaldehyde Induced Arthritis In Rats.

Groups	Increase in joint diameter (mm)		
	8th day	9th day	10th day
Control(Vehicle)	3.516±0.175	3.658±0.374	3.708±0.329
Standard(Meloxicam)	1.066±0.121	1.116±0.213	1.166±0.136
Test (Meloxicam+Majoon suranjan)	1.933±0.081**	1.925±0.172**	2.016±0.160**

*** Significantly different from standard at p<0.01*

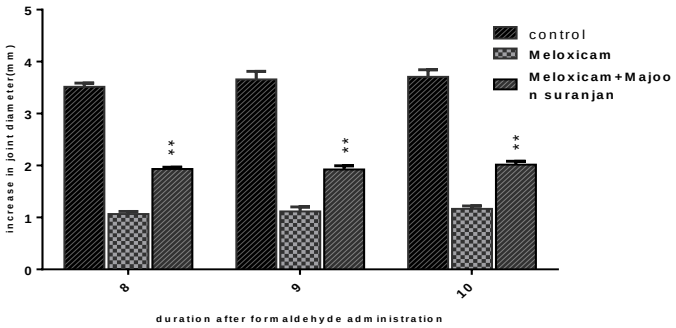

Fig 2 : Formaldehyde Induced Arthritis In Rats.

** significant at $p<0.01$

Adjuvant Induced Arthritis

The increase in joint diameter was found to be significantly low of Group II and Group III when compared to Group I (control). But increase in joint diameter is more in Group III when compared to Group II in Turkey's multiple comparison and it is significant at $p<0.05$.

Table 3: Adjuvant Induced Arthritis in Rats

Groups	Increase in joint diameter (mm)		
	7th day	14th day	21th day
Control(Vehicle)	4.94±0.14	5±0.12	5.08±0.11
Standard(Meloxicam)	1.38±0.16	1.49±0.18	1.44±0.18
Test (Meloxicam+Majoon suranjan)	2.45±0.26**	2.45±0.18**	2.41±0.10**

** Significantly different from standard at $p<0.01$

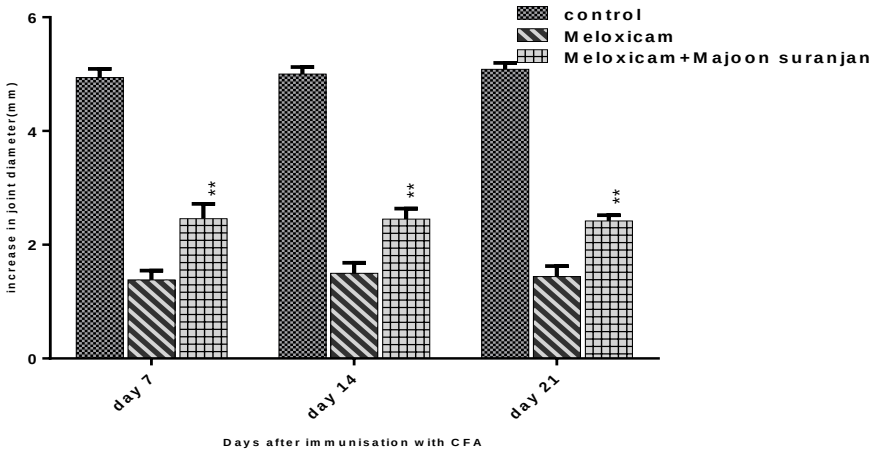

Fig 3: Adjuvant Induced Arthritis In Rats

** Significant at $p<0.01$

DISCUSSION

Herb-drug interactions can occur in several different ways. Pharmacodynamics interactions occur when the object drug's effect is altered by the interfering drug or herb. These interactions are not due to an alteration in the plasma concentration of either drug but rather because of the net effect that can be additive, synergistic (together the two drugs can achieve better results than the sum of their two actions alone) or antagonistic. These adjectives can refer to alteration in the object drug's intended therapeutic effect, or can refer to the change in the toxicity levels and adverse side-effects as well. On the other hand, pharmacokinetic interactions denote changes in the absorption, distribution, metabolism or elimination of the object drug due to the presence of the interfering drug. Unlike Pharmacodynamics interactions, these interactions do result in changes in the plasma concentration of the object drug, and as a consequence, the toxic or sub-therapeutic levels occur more frequently [22].

Majoon Suranjan (MS) is a Polyherbal formulation that is used in the Unani system of medicine for treatment of RA and other joint disorders [23]. It is composed of the extracts of 18 individual medicinal plants which are formulated in a sugar base. Some of the individual constituents of this polyherbal formulation have been evaluated for their anti-inflammatory activity. Lawsonia innermis has been shown to be efficacious in cotton pellet granuloma, granuloma pouch and formalin induced paw oedema models of inflammation in rats showing anti-inflammatory activity [31]. Chebulagic acid from the immature fruit of Terminalia chebula has been shown to suppress the onset and progression of collagen induced arthritis in mice 24]. Colchicum leuteum has been shown to afford symptomatic relief in patients with rheumatoid arthritis in a 90 day trial [25,26]. Coriandrum sativum has been shown to be efficacious in reducing carrageenan induced paw oedema [27], Pyrethrum indicum has been shown to induce synoviocytes apoptosis and suppress proliferation of synoviocytes in adjuvant-induced arthritis rats [28], Zingiber officinalis has been shown to decrease pain and swelling in arthritis patients [29], and Foeniculum vulgare has been found to be effective in reducing carrageenan induced paw oedema [30].

Meloxicam is a nonsteroidal anti-inflammatory drug that iscurrently being used in both human and veterinary medicine [31, 32].

In the present study, comparison in inhibition of turpentine oil induced paw edema was observed in both meloxicam and meloxicam+majoon Suranjan treated group was observed throughout the observation period.

Majoon Suranjan influences all the phases of turpentine induced inflammation in the rat paw. Majoon Suranjan shows inhibition of paw edema during the late phase of inflammation showing prominent cyclooxygenase/lipoxygenase inhibitory activity[41]. The combination use of meloxicam with majoon Suranjan shows the inhibition of paw edema during the initial and intermediate phase of inflammation comparable to meloxicam. But the inhibition of paw edema of combination therapy during the late phase of inflammation is significantly more when compared to meloxicam single treatment. This suggests an additive effect by the polyherbal combination with that of meloxicam in inflammation.

In formaldehyde induced inflammatory arthritis combined dose of meloxicam was able to significantly reduce the joint swelling when compared to control. However the reduction in joint swelling in meloxicam+majoon Suranjan treated group was significantly less when compared to meloxicam treated group. This suggests the decrease in anti-arthritic efficacy of meloxicam when combined with majoon Suranjan. The result may be due to the induction of drug metabolizing enzymes of meloxicam by the individual constituents of polyherbal formulation during the long term use of the combination therapy or either may be due to the alteration in the absorption of the drug.

The decrease in efficacy of meloxicam may be due to the alteration in the inflammatory mechanism of meloxicam in formaldehyde induced inflammatory arthritis by the majoonsuranjan.

Complete Freund's adjuvant induced arthritis is one of the most widely used models as it has been shown to share a number of clinical and immunological features with human arthritis [33].Therefore, this model is used with a relatively high degree of validity for evaluating agents with potential antiarthritic activity.in this model in the vehicle treated animals (control), there was an increase in the joint diameter after day 14, which can be attributed to the delayed immunological flare in the disease [34]. In previous studies on majoonsuranjan showed delayed inhibition in joint diameter in this model [35].

CONCLUSION

In present study effects on antiarthritic potential of meloxicam by the majoonsuranjan was evaluated throughout the observation period of the studty. Majoonsuranjan combined treated group shows significant inhibition of joint swelling in rats when compared to the control or vehicle treated group. However thereis a less delayed inhibition in joint swelling of meloxicam+majoonsuranjan combined treated group when compared to meloxicam treated group.

It suggests that the reason for reduced joint swelling in combination therapy may be due to the alteration in the absorption or metabolism of either meloxicam or majoonsuranjan or both when used concomitantly. It inferred that the long term combination use of herbal or polyherbal formulation with that of allopathic drug doesn't shows the beneficial effect and may lead to decrease in efficacy of the drugs due to alteration in pharmacodynamics and pharmacokinetic properties.

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