

## NATURAL ORAL FORMULATION OF MEDORRHINUM MICRO-DROPLETS COMPOSITES FOR CHRONIC RHEUMATOID ARTHRITIS

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### ABSTRACT

**Objective:** An innovated, compatible, and complete cure of Rheumatoid arthritis through Medorrhinum extract formulated with natural encapsulated fruit (Raisin) without incorporating any outside ingredients. This is first orally chewable natural fruit capsule with naturally fruit inbuilt preservative. It totally eradicates disease by empowering autoimmune system with natural medication adherence for patients. **Materials and Method:** This drug was cultured, extracted, isolated, purified, concentrated, formulated, therapeutically validated & evaluated in mice. Therapeutic effects were evaluated in 3 mice group- without drugs, with 1 drop & with 2 drops administration to identify retention/holding time of mice in rotating Rota rod. And clinically designed & tested in 18 acute & chronic patients. **Result and**

**Discussion:** Its therapeutic index is very high, because the effective drug concentrated in doses (2 drops) recommended for adult human itself is found to be safe for mice. The intraday mean value retention/holding time (i.e., to understand the improvement in mobility on rectifying articulate joints defects) on the three groups (each group has 3 mice) from 9:30 am – 2:30 pm on 1hr interval of mice showing the mean values of  $5.17 \pm 0.89$ ,  $43.03 \pm 1.69$ ,  $74.25 \pm 1.55$  (in Sec.). The inter-day mean value retention/holding time on three consecutive days was evaluated showing a vast difference which mean to be highly improved healing status with dates. **Conclusion:** Medorrhinum is naturally formulated in fruit Raisin, which is found to be safe without any adverse & side effects on evaluating in mice. On clinical

investigation it seems to be compatible with natural medication adherence for patients. The drug was successfully evaluated for its safeties in mice on same dose referred to human. On formulation which also sounds natural good medicine adherence. This formulation clinically completely heals patients and assist no chance for disease returns.

**KEYWORDS:** Lethal dose test Safety, Raisin fruit formulation, Animal studies, irreversible Anti-rheumatic arthritis.

## INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease in which the body's immune system – which normally protects its health by attacking foreign substances like bacteria and viruses – mistakenly attacks the joints. This creates inflammation that causes the tissue that lines the inside of joints (the synovium) to thicken, resulting in swelling and pain in and around the joints. Our understanding of the pathology and management of rheumatoid arthritis (RA) has evolved significantly over last two decades. Since the 1990's it was known that irreversible joint damage occurred early in the disease and hence early use of DMARDs was recommended.<sup>[1]</sup> Despite the available knowledge managing patients of rheumatoid arthritis was always a challenge. The textbook criteria for diagnosing the disease hardly seemed helpful in identifying early disease.<sup>[2]</sup> The use of sequential monotherapy resulted in relatively poor remission rates.<sup>[3]</sup> The evaluation of patients was mainly focussed on musculoskeletal manifestations and other systemic complications which were often missed.<sup>[4]</sup>

A new evidence-based, pharmacologic treatment guideline for rheumatoid arthritis (RA) was develop. Systematic reviews to synthesize the evidence for the benefits and harms of various treatment options has been conducted. Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate the quality of evidence has been used. The guideline covers the use of traditional disease-modifying antirheumatic drugs (DMARDs), biologic agents, *tofacitinib*, and glucocorticoids in early (<6 months) and established (6 months) RA. In addition, it provides recommendations on using a treat-to-target approach, tapering and discontinuing medications, and the use of biologic agents and DMARDs in patients with hepatitis, congestive heart failure, malignancy, and serious infections. The guideline addresses the use of vaccines in patients starting/receiving DMARDs or biologic agents, screening for tuberculosis in patients starting/receiving biologic agents or *tofacitinib*, and laboratory monitoring for traditional DMARDs. The guideline includes 74 recommendations: 23% are strong and 77% are conditional. This RA guideline

should serve as a tool for clinicians and patients for pharmacologic treatment decisions in commonly encountered clinical situations. These recommendations are not prescriptive, and the treatment decisions should be made by physicians and patients through a shared decision-making process taking into account patients' values, preferences, and comorbidities. These recommendations should not be used to limit or deny access to therapies.<sup>[5-9]</sup>

A powerful and deep-acting medicine, often indicated for chronic ailments due to suppressed gonorrhœa. For women with chronic pelvic disorders. Chronic *rheumatism*. Great disturbance and irritability of nervous system. Pains intolerable; tensive; nerves quiver and tingle. Children dwarfed and stunted. Chronic catarrhal conditions in children. Nose dirty, tonsils enlarged, thick yellow mucus from nostrils; lips thickened from mouth breathing. State of collapse and *trembling all over*. History of sycosis. Often restores a gonorrhœal discharge. Intensity of all sensations. Edema of limbs; dropsy of serous sacs. Disseminated sclerosis.<sup>[10,11]</sup>

*Medorrhinum*, an attenuated preparation from the gonococcal discharge, which develops due to gonococci, is a far-reaching remedy of multi-miasmatic type often missed in practice. The statements, 'Nosode is not always a nosode' and 'it has in its stock, beyond the ken of antimiasmatic and intercurrent usage, acute and chronic dimensions', aptly apply to Med.

A nosode is a blend of the disease-potential and the host-response; hence, it represents the dynamic potential of germ, host and their inter-action to become the powerful and complex healing force to meet the inveterate morbid conditions. Med. is characteristic in a way that host response is almost minimally represented in gonococcal pus from which Med. is prepared.<sup>[12-16]</sup>

Exciting advances in the understanding of rheumatoid arthritis (RA) and its pathogenesis are providing new hope for those suffering from this debilitating disease. A currently incurable autoimmune disorder, RA is one of the most common forms of inflammatory arthritis, causing suffering, disability (90% within 20 years will become clinically disabled), and even premature death. Many of the past and current therapies offer little more than symptomatic relief.<sup>[17]</sup> Even the so-called disease modifying antirheumatic drugs (DMARDs) do not halt the progression of this disease, but rather decrease the onset of disability by 30%.<sup>[18]</sup> Recent research into the complex and varied components of this disease is leading to the development of more effective targets for pharmacological approach than ever before. Ongoing deeply into the RA management, therapy was tried to develop upto its end point

termination and irreversible return marks. Till date there was no drugs & medicines which tells good-bye to RA. Instead of that patients has to compromise with supportive treatment. Also, this research spell out the chance newly compatible natural fruit as shell formulation instead of synthetic capsules. The crude drug Medorrhinum was evaluated for its therapeutic index in mice and compatibility with efficacy to 19 patients volunteers.

## MATERIALS AND METHODS

### Selection of dosage formulation

The dosage are usually selected according to its % of effectiveness, compatibility easy to take. But, here another benefit is reinforced, i.e. medication adherence to patients. Patients like to take dosage if it's seems to be palatable and healthier to them. So, grapes was selected which satisfies the above requirements. And the grapes were allowed to dry later sustaining the injected into it and further acts as preservative dosage form.

### Acquisition to Natural formulation

The skin consists of an outer layer covering the berry. It is made up of six to ten layers of thick walled cells. The outer surface of the skin is covered with a wax-like coating called the cuticle, which renders the berry waterproof. The main components in the skin are: coloring matter (red and yellow pigments), tannins, aromatic substances, and potassium and other minerals.

**a) Chemical Composition:** Freshly expressed grape juice consists of 70 to 80% water and many dissolved solids. These soluble solids include numerous organic and inorganic compounds like- Sugars, organic acids, phenolic compounds, nitrogenous compounds, aroma compound, minerals, pectin substances.

**b) Sugars:** In grapes, a large portion of the soluble solid is sugars. Glucose and fructose are the main sugars in the juice. The sugar content of the juice of ripe grapes varies between 150 to 250 g/L. In unripe berries, glucose is the predominant sugar. At the ripening stage, glucose and fructose are usually present in equal amounts (1:1 ratio).

**c) Preservative:** The principal organic acids found in grapes are tartaric, malic, and to a small extent, citric.

**Extraction of crude drugs**

Medorrhinum is an attenuated bacterium *Neisseria gonorrhoeae* extract obtained from pure cultured male urine pus suffering patients.

**A] Steps for nosode preparation:** In case of organism (may include bacteria, virus, protozoa, parasites, or fungi) or other biological material sourced from academic or commercial source, it must be documented accordingly.

- Source material/Strain: To use the latest virulent or standard strains of organisms (culture, whenever possible), resistant strains, combinations of various strains.
- Organism count: The count of the organism in the source material or in the mother source must be specified, achievable, and significant. The recommended organism count for making the nosodes suggested in HPI (Homoeopathy Pharmacopeia of India) is 20 billion.<sup>[17]</sup>
- Ethical consideration: In case the blood samples are drawn from volunteers, informed consent form must be served to him/her declaring the proposed use of the sample. Ethical guidelines for biosafety.<sup>[18]</sup>

**B] Nature of material:** Depending on the nature of material, whether organism are capable of producing endotoxins, exotoxins, made from purified toxins or made from microbes, viruses, or clinical material from diseased subjects, these preparations are divided in HPI into four groups<sup>[19]</sup> N-I, - II, - III, and -IV.<sup>[20]</sup> So, it comes under N-I—Preparations made from lysate of Micro-organism capable of producing bacterial endotoxins.

**C] Removal/Separation of other components:** In case of any nosode sourced from serum, serum expression, centrifugation, and/or filtration can be used to procure the organism from the source material. The samples were subjected to centrifugation to obtain clear serum and filtration (Seitz filter) to get rid of cell debris, unidentified bacteria, and large protein particles.

**D] Characterization of source material:** The microorganisms need to be characterized in terms of genotyping and strains, as per the latest available technology eg., *Medorrhinum animalcule*.

**E] Safety:** The safety of nosode in various potencies must be established as per the sterility testing mentioned in Indian Pharmacopoeia or European Pharmacopoeia<sup>[21]</sup> for aerobic and anaerobic organisms.<sup>[22]</sup>

**F] Mother preparation:** At this stage, specified quantity of pure culture of one strain or more (polyvalent) nosode or more than one type of organisms can be mixed in vehicle to obtain original stock nosode. Vehicle: Water for injection that is free from organisms, pyrogens and NaCl is recommended as preferred vehicle.

**G] Quantification:** It should be considered mandatory to specify the strength of stock nosode, whenever technology is available. Organism count is to be done by the digital counters, turbidity match method, or as specified in individual monograph.

**H] Potentization: Machine and method:** Succession (the condition of being shaken especially with violence): The method of potentization is decided depending on the nature of source material. Succession is recommended over trituration for the microorganisms that are found in micron size, which are generally uniformly spread in the solution, which should be applicable to nosodes sourced from bacteria.

### Designing to formulate

The crude drug is formulated into natural solid dosage form i.e., dried grapes (Raisin). The material required are grapes, micro-syringe, Brine-salt, de-humidifiers, desiccator, air-tight container.

- a) The concentrated amount of crude drug extract in ethanol was taken in a micro syringe and injected on 4 groups of 10 hybrids grapes from removed stalk edged.
- b) Out of 4 groups of 10 grapes- one group is stored in direct brine-salt crystals; one group was stored in 60% salt water; one group is stored under 67% saturated sugar solution and last group in desiccator with de-humidifier knob attachment for the purpose of plasmolysis.
- c) The grapes were left for couple a week and was under observation till its dry.
- d) From each groups of grapes one were crushed and feed them in two groups among three where 3 in each group.
- e) Then the physiological activities were noted under the Rota meter.
- f) This will reflects the drug- active constituent interactions of the dried grapes (Raisin).



## RESULTS AND DISCUSSIONS

### Animal Effective doses assay

Medorrhinum is used for decades as homeopathic medicine. We have gone through animal assay over 1-3 drops which is to be injected on grapes/ Raisin especially plan for human being whose body surface area and weight is 100 times greater than mice's. So, in that contest it's easy to identify the lethal dose for human if comparing the activity of same dose in mice as well.

#### a) Lethal dose design

Thus, fifteen (15) mice were taken and divided into three (03), each group having five (05) mice. First group of mice was administered with 1 drop, similarly 2<sup>nd</sup> group of mice have given two (02) drops and 3<sup>rd</sup> group with three (03). The survival, mortality and morbidity rate was evaluated. It was discovered in all conditions the all mice are surviving.

The drugs were evaluated by two major ways in Figure-1(A&B) – first by orally drop wise administering the drugs from the bottle dropper and through mice feeding pipe as per the effective drop doses & concentration recommended for an adult healthy human volunteers.

The drugs which is injected in Raisin were crushed in Figure-1(C) on looking feeding compatibility and feeds to each targeted mice with help of cannula in Figure-1(D).

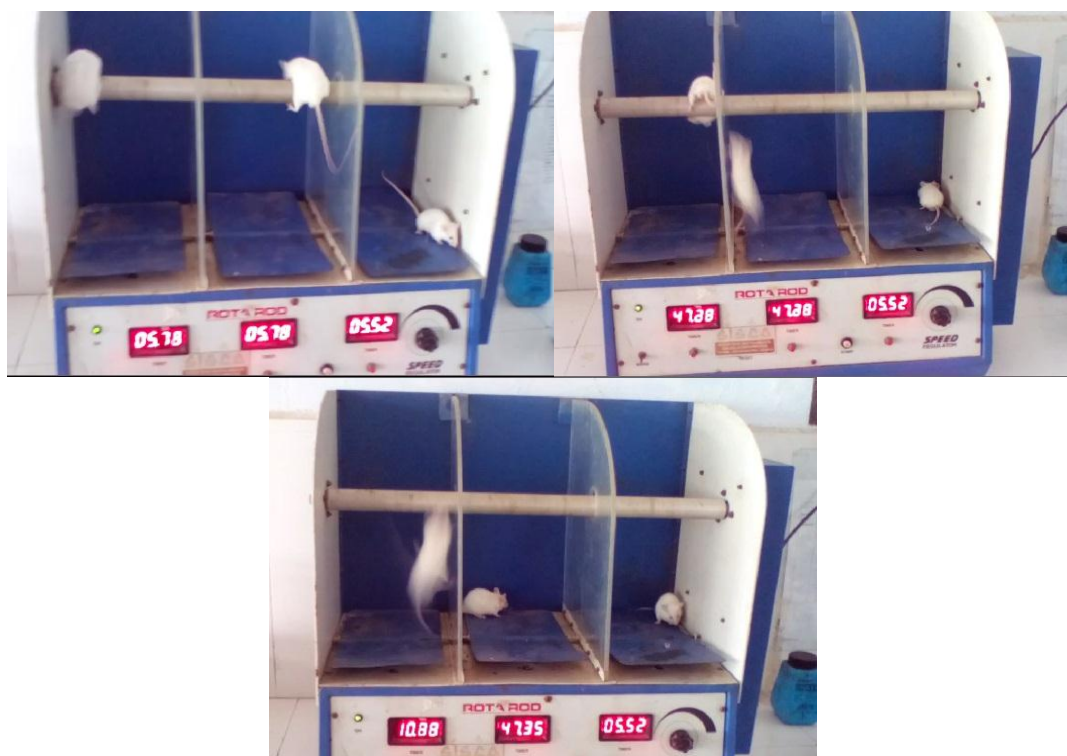


**Figure 1: Images representation of - A&B) Direct drug feeding of mice from solution in drops; C) Crushing of injected drug in Raisin; D) Feeding of crushed raisin drug from portion of B image.**

**b) Therapeutic Evaluation**

In very first the mice were feeds with more protein diet with less drinking water. So, that the by-product of nitrogen waste was readily been accumulated as Ammonia, urea and uric acid. The uric acid crystal accumulated on joints. And thus the limbs movement is restricted and painful in arthritic condition. Out of normal mice Rheumatoid arthritis mice were selected as per evaluating their movement as well as notifying exercising mode on rota- rod crawling. While moving through the therapeutic evaluation, the mice were grouped according to the dose as concern. Where, one group is without drugs, 2<sup>nd</sup> group is given one drop of drug and 3<sup>rd</sup> group was administered with two drops of drugs.

On Figure-2, three images showing the consecutive falling of mice from Rota rod in three different state in three different selected RA group. First group of RA mice which was putted in rotating Rota rod without any drug (blank) falls within the time range of 4-6 Sec holding time approximately. And the 2<sup>nd</sup> group of mice with administered 1 (one) drop of drug persist the holding time range between 45-55 sec. Finally, the 3<sup>rd</sup> group of mice with administered 2 (two) drops of drug solution shows the holding time range between 70-80 sec. This means the 2 (two) drops of drug solution reveals the perfect dose for treating RA as per the times and duration is concerned in Table-1.



**Figure 2: Improving holding & retention capacity of different group of mice on revolving Rota rod.**



### Estimation of RA activity in Mice group

For evaluation of RA activities on mice, RA mice were selected and grouped under three groups- without drugs, with one drop of targeted drug & with two drops of targeted drug. And each group of mice where having 3 mice. These RA mice were feeds with drugs before for 30 days and their recovery activities were evaluated (inter-day & intraday) on rota-rod apparatus, were retention time of mice over the revolving rod has been estimated as per their effect and recovery.

The intraday mean value retention/holding time on the three groups (each group as 3 mice) from 9:30 am – 2:30 pm on 1hr interval of mice showing the mean values of  $5.17 \pm 0.89$ ,  $43.03 \pm 1.69$ ,  $74.25 \pm 1.55$  (in Sec.) against without drugs, with 1 drop & with 2 drops respectively represented on Table-1. The same is plotted in Figure-3 to present the different healing level of mice in compare to the blank (Without drugs).

**Table 1: Intraday Rota rod retention time reading among three group of mice as per drug dose & without drug**

Sl. No.	Group of Mice (3 mice in each group)	Intraday Reading (in Sec)					
		9:30am	10:30am	11:30am	12:30pm	2:30pm	Mean
1	Without drug	$5.52 \pm 0.23$	$5.41 \pm 1.29$	$4.94 \pm 1.13$	$5.12 \pm 0.15$	$4.86 \pm 1.69$	$5.17 \pm 0.89$
2	With one drop	$47.38 \pm 1.66$	$45.38 \pm 1.45$	$42.31 \pm 1.23$	$40.71 \pm 1.89$	$39.38 \pm 2.22$	$43.03 \pm 1.69$
3	With two drops	$77.38 \pm 1.34$	$75.33 \pm 1.51$	$76.32 \pm 1.33$	$74.38 \pm 1.59$	$67.88 \pm 1.99$	$74.25 \pm 1.55$

Similarly, the mean values of all intraday evaluation was aggregated on three consecutive days to earn the mean values of these three groups in same time 9:30am in Table -2. This shows the differences plotted on histogram in Figure-4, conveys the healing effects of drugs time to time and day to day.

**Table 2: Consecutive Inter-days assessment of mean readings of three group of mice.**

Sl. No.	Inter-day reading & timing	Mean readings of inter-day assessment		
		Without drugs	With one drop	With 2 drops
1	Wednesday (9:30am)	$5.17 \pm 0.89$	$43.03 \pm 1.69$	$74.25 \pm 1.55$
2	Thursday (9:30am)	$7.63 \pm 0.97$	$49.19 \pm 0.77$	$78 \pm 2.05$
3	Friday (9:30am)	$10.34 \pm 0.47$	$56.25 \pm 2.11$	$82.54 \pm 2.62$

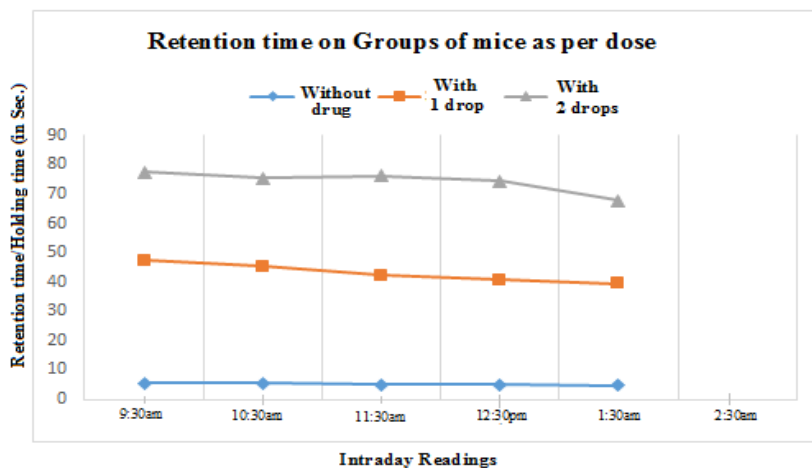


Figure 3: Difference in mean value retention times between three groups.

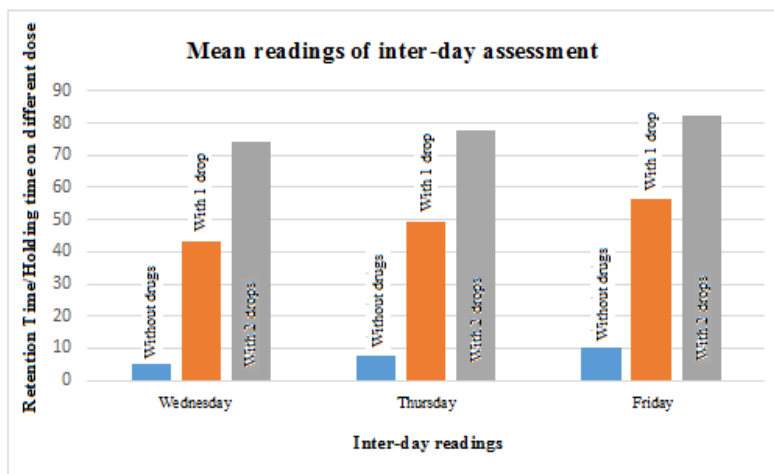


Figure 4: Comparative retention time mean readings on inter-day evaluation.

**Assessment of patient’s medication history and recovery**

The patients were selected according to the criteria: The age factor between 40-60, suffering from Rheumatic Arthritis, joint pain, joint immobility and swelling etc. These patients are undergoing treatment in hospital at acute as well as chronic level as per Table-3.

Table 3: Selected patients medical history before treatment with targeted drug, Medorrinum.

Group of Patients [IP-No]	Sign & Symptoms	Diagnosis	Treatment (Medication & non-medicated)	Side-effects	Status
Grp-1: Ortho- 4439,5853, 7234,7239, 8323,9666	stiff joints, Fluid enters the joint, Inflammation, fatigue, sickness	Problem with immune system, Abnormal increase Rheumatoid Factor [RF], high C-reactive protein (CRP) levels	Minocin, Azathioprine, diclofenac with misoprostol & Aspirin. and Bed rest	minocycline can cause discoloration of the skin, Common Cardiac problem and GIT discomfort from NSAID	Treatment continues for RA Management.
Grp-2: Ortho-2395, 3179,3256, 4238, 6598,7745, 8349,84329	Joint stiffness & fatigue in knees, swelling, pain on walking, weight loss	Elevated Anti CCP (anti-cyclic citrullina- ted peptide); increase RF.	Methotrexate [DMARD], Ibuprofen, Cyclosporin, Leflunomide And Physiotherapy	Leflunomide cause diarrhea, Methotrexate cause liver,bone marrow and birth defect.	Treatment continues along with Physiotherapy.
Grp-3: Ortho- 1142, 3287, 5632, 6667, 6712	Immobility of joints, tremendous pain, reddens and heat, Swellings. Much worst condition in cold AC/ Winter. Restlessness with insomnia.	Positive HLA-B27 test, high creatine phosphokinase (CPK) and aldolase, Decreased levels of various components of complement -- C3, C4, or CH50,high ANA, or antinuclear antibodies, asculitis.	Tolmetin, Naproxen, Celecoxib, triamcinolone, Abatacept And Surgery	Tolmetin has Nausea, vomiting, heartburn, dizziness, drowsiness, diarrhea. Abatacept side- effects Headache, nausea, or cold symptoms. Naproxen has Belching, bruising difficult or labored breathing. Celecoxib has Cough, fever, skin rash, sneezing, sore throat, swelling of the face, fingers, feet, or lower legs. Triamcinolone has Aggression, Agitation, anxiety, blurred vision, decrease in the amount of urine, dizziness, fast, slow, pounding, or irregular heartbeat or pulse, headache irritability, mental depression, mood changes, nervousness, noisy, rattling breathing, numbness or tingling in the arms or legs, pounding in the ears, shortness of breath, swelling of the fingers, hands, feet, or lower legs, trouble thinking, speaking, or walking, troubled breathing at rest, weight gain	Treatment continue as post operative surgery.

The patients were sub-divided into three (03) groups as per their chief complains, clinical history and treatment. The above table represents the brief results of Anti-inflammatory, DMARD, Immunosuppressant, steroids and various enzyme inhibitors. But the reports always shows the managing and repairing mode instead of complete treatment.

### Treatment and its continuation

The above group of patients after getting fed-up with the treatment outcomes, comes for counseling (Figure-5) about the new formulation of new drug Medorrhinum. And with their interest, on behalves of patient consent letter they tried the new treatment. According to this treatment each raisin formulation consist of two drop of Medorrhinum 1:200 dilution in 45% alcohol. And each patients have taken / chew 1 raisin OD everyday upto 7-10 days as per the severity. The dose is gradually inclined as per Table-4.

**Table 4: Dose designed & recommended for drug treatment and response evaluated.**

Sl. No.	Diseased Condition	Doses							
		1 <sup>st</sup> week	next15days	1month	Next 3 Month	Next 6 Month	Next 12 Month	Next 1.5 Years	Next 2 Years
1	Mild (Grp-1)	1every day	1after every day 1days	Weekly two	8 every month	4 every month	2 every month	Patient Recovered	-----
2	Moderate(Grp-2)	1every day	1after every day 1days	Weekly three	10 every month	6 every month	4 every month	2 every month	Patient Recovered
3	Severe(Grp-3)	1every day	1after every day 1days	Weekly three	12 every month	8 every month	5 every month	5 every month	Patient Recovered But 3 per year

The total 100% cure from this disease is due to external stimuli by the drug for the production of intrinsic antibody to combat against responsible antigens. And also by increasing the tolerance capacity of cartilaginous tissue with successful control over the inflammatory mediators.



**Figure 5: Clinical oral administration of new encapsulated drug in raisin to RA.**

## CONCLUSION

The Anti-Rheumatic drug Medorrinum was showing no lethal effects even in overdose. This drug is extracted, concentrated, formulated in natural encapsulated fruit (Raisin). Its effectiveness is miraculous in Mice form complete cure. In human patient volunteers, under mild, moderate and severe diseased condition it completely cures RA for acute and chronic patients. In future, there would be a definite chance to emerge a synthetic molecules on its resemblance. Also, the natural encapsulation would be a future prospects for most of the compatible drugs.

## Abbreviations

Rheumatoid arthritis – RA; Once daily- OD; Disease modified Anti-rheumatoid drugs- DMARD; Grading of Recommendation, Development & Evaluation- GRADE.

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