Nutrafoods (2019) 2 95-99. DOI 10.17470/NF-019-0013

Original Research

Analgesic effects of RodeMyr®, a *Commiphora molmol* extract with a highly standardized furanodiene content

Abstract

Furanoeudesma-1,3-diene, curzerene and lindestrene are thought to be the active principles underlying the analgesic action of myrrh (*Commiphora molmol*) extract. Recently, a very highly standardized dry extract from myrrh has been developed (RodeMyr®) and formulated in a single active nutritional supplement (Mirra+®), notified to the Italian Health Authorities in 2018. We have therefore used such a finished product to evaluate the analgesic action of myrrh in subjects affected by chronic pain.

The results of the study have shown that the use of 100 mg of dry myrrh extract, administered twice a day, is effective in reducing pain perception and *functio laesa* both as a sole and an add-on therapy.

Tolerability, compliance and side effect evaluation demonstrated the safety profile of the extract and its usefulness in treating patients with chronic pain.

Francesco Di Pierro [1*]

Alexander Bertuccioli [2]

Rosanna Giuberti [3]

[1] Scientific Department, Velleja Research, Milan, Italy

[2] D.I.S.B., Urbino, Italy

[3] S.I.C.T., Milan, Italy

*Corresponding author:
Francesco Di Pierro
f.dipierro@vellejaresearch.com

Keywords: Myrrh, arthrosis, botanicals, pain

Introduction

According to the 2014 ESCOP Monographs [1], myrrh is a gum-resin, hardened in air, obtained by incision or produced by spontaneous exudation from the stem and branches of *Commiphora molmol* Engler and/or other species of *Commiphora*. Species other than *Commiphora molmol* which may be acceptable sources of medicinal myrrh include *Commiphora abyssinica* and *C. schimperi* [2]. From a chemical perspective, myrrh consists of three major components: volatile oil (2–10%), resin (25–40%) and gum (30–60%) [3]. The main constituents of the volatile oil are furanosesquiterpenes of various structural types, including furanoeudesma-1,3-diene, furanoeudesma-1,4-diene-6-one, lindestrene, curzerene, curzerenone, furanodiene, 2-methoxyfuranodiene and 4,5-dihydrofuranodiene-6-one, together with sesquiterpenes such as α-copaene, elemene and bourbonene [4]. Characteristic molecules within the resin are α-, β- and γ-commiphoric acids, α- and β-heerabomyrrhols, heeraboresene and burseracin, in addition to various terpenes and a sesquiterpene lactone, commiferin [5, 6]. The water-soluble gum is composed of a hetero-disperse mixture of proteoglycans in which chains of alternating galactose and 4-O-methylglucuronic acid, and separate chains of arabinose, are attached to the protein moieties via hydroxyproline linkages [3]. The curzerene, furanoeudesma-1,3-diene and lindestrene content in myrrh is primarily responsible for the myrrh aroma as well as the analgesic activity of myrrh [7].

Analgesics are one of the most widely prescribed classes of drugs to relieve pain and also one of the most common causes of serious side effects and dependency [8]. Due to this, there is a continuing need for new remedies that are able to work as painkillers which are characterized by a better safety profile. Myrrh has been used as a wound-healer and painkiller since ancient times, with medicinal uses dating back to Biblical times [9]; at the same time, ethnopharmacological evidence suggests that myrrh has been extensively used both internally and externally without serious adverse effects [10]. For these reasons, myrrh extracts could be considered to be excellent candidates for developing new analgesic botanicals.

Recently, a myrrh extract branded MyrLiq® demonstrated an ability to counteract pain of various origins [11]. A direct comparison with some of the most frequently used drugs revealed that the product had similar effects, although it required a longer course of treatment of approximately 20 days and a daily dose between 200 and 400 mg to obtain a significant effect, especially in male patients. We have thus decided to clinically evaluate a new highly standardized dry extract of myrrh to evaluate whether a different manufacturing process and chemical profile could generate a product that is effective at a lower dose and/or as an adjuvant therapy in order to reduce the dosage of synthetic analgesic drugs.

Materials and methods

Tested product

RodeMyr®, a dry extract of myrrh (total furanodienes: >3%; including furanoeudesma-1,3-diene >30%, β-elemene >20%, curzerene >10%, lindestrene >10%, curzerenone >10%, others >10%), was kindly provided by Rode Pharma S.r.l. (Casale Monferrato, AL, Italy). Identification and quantification of furanodienes was performed by GC-MS/FID and internal standards and proprietary methods were used.

Mirra+®, the finished product containing a dry extract of myrrh, was kindly provided by International Sport Nutrition S.r.l., PD, Italy after manufacturing in the facility located at Chiesanuova, San Marino Republic. The finished product, containing 100 mg of RodeMyr® per

capsule, was notified to the Italian Health Authorities in 2018 and is number 117476 in the list of nutritional supplements [12].

Study population and criteria

To assess the product (Mirra+®) effects, a group of subjects consisting of 32 men and 34 women was enrolled. The trial was conducted in an outpatient clinic located in Milan under the supervision of a medical doctor and in accordance with the Declaration of Helsinki. Each participant was told the study procedures and objectives and signed an informed consent and a form covering personal data handled in accordance with privacy law. The inclusion criteria were people aged between 18 and 60 with a diagnosis of chronic pain affecting muscles, joints or the back, due to sports trauma or advanced age. Exclusion criteria included: being aged below 18 or over 60; the presence of a neurological disorder, heart, vascular, lung or kidney disease, or a severe metabolic disorder; muscle pain of iatrogenic origin; a past or current history of cancer; presence of any type of immunosuppression; and refusal to sign the informed consent and/or the privacy form.

Study trial

This was an observational, open, pilot study to verify the analgesic properties of a nutritional supplement containing RodeMyr® at a dose of 100 mg/capsule administered twice a day, every 12 hours, on an empty stomach. Enrolled subjects could already be receiving treatment with conventional analgesic drugs (diclofenac, nimesulide, ketoprofen, ibuprofen, acetaminophen, naproxen, tramadol, ketorolac). Subjects already undergoing treatment with analgesics, very often receiving treatment with proton pump inhibitors also, could have received the tested product as an adjuvant therapy. Myrrh therapy, alone or as an add-on, lasted 10 days, according to the established protocol. The following parameters were evaluated at baseline and at 3 (T3), 6 (T6) and 10 (T10) days after initiation of the treatment protocol: pain perception, estimated according to the visual analogue scale (VAS) devised by Scott–Huskisson (from 0 = none to 10 = intolerable) [13] and *functio laesa*, scored by an arbitrary scale ranging from 0 = complete physical function to 10 = maximum impairment of physical function. Treatment tolerability (ranked as poor, fair, good), compliance (ranked as poor, fair, good), and adverse events were also evaluated. Tolerability and compliance scores between 0 and 3 corresponded to poor, between 4 and 7 to fair and between 8 and 10 to good.

Statistical analysis

Data were described using descriptive statistics (mean and standard deviation for continuous variables; percentages for categorical variables) and exploratory comparisons were performed by applying the non-parametric one-way ANOVA on ranks test or Fisher's exact test, as appropriate. A p value < 0.05 was considered statistically significant.

Results

According to the study protocol, subjects were divided into 3 different groups:

1) subjects (N=18) already undergoing treatment with analgesic drugs who did not receive the additional myrrh product;

2) subjects (N=22) already undergoing treatment with analgesic drugs who did receive the additional myrrh product;

3) subjects (N=26) with a new diagnosis of non-severe chronic pain, who were administered the myrrh product.

The 3 groups of subjects were found to completely overlap in terms of age and sex, and no statistically significant differences were observed (data not shown). No differences regarding the time from initial diagnosis were observed between groups 1 and 2 (data not

shown). As expected (**see Table 1**), subjects with chronic pain and already undergoing treatment with conventional analgesics demonstrated quite stable clinical scores during the 10 days of evaluation. Tolerability and compliance were stable and mainly affected by gastric pain and sleep disturbance as the main side effects.

Table 1 Results° observed in subjects (N=18) already undergoing treatment with analgesic drugs with no addition of the myrrh product

	T=0	T=3	T=6	T=10
Pain perception ^	5.8±2.2	7.1±2.7	6.4±1.9	6.8±2.4
Functio laesa^	4.2±1.5	5.5±3.3	4.9±2.3	5.0±2.6
Tolerability	poor	poor	poor	poor
Compliance	fair	fair	fair	fair
Side effects *	6/18	5/18	4/18	7/18

°No statistical differences were detected.
*****Main side effects reported were gastric burning and difficulty in falling asleep; values are expressed as the number of subjects with a side effect over the total number of subjects.
^ Values are expressed as the mean ± standard deviation

In contrast, as shown in **Table 2**, the add-on therapy consisting of the myrrh product administered at a dose of 100 mg twice a day brought about a clear improvement in symptoms and signs of chronic pain, with a reduction in these of more than 30% and approximately 50% after 3 and 6 days, respectively, of adjuvant therapy.

Table 2 Results observed in subjects (N=22) already undergoing treatment with analgesic drugs with addition of the myrrh product at a dose of 100 mg twice a day

	T=0	T=3	T=6	T=10
Pain perception ^	6.1±1.8	4.0±1.5°	3.2±1.2°	2.8±0.8°°
Functio laesa^	5.0±2.5	4.6±2.9	4.0±2.0°	3.9±1.8°
Tolerability	poor	fair	fair	good
Compliance	fair	good	good	good
Side effects *	8/22	7/22	4/22°	3/22°

°p<0.05 versus T=0; °°p<0.01 versus T=0.

***** Main side effects reported were gastric burning and difficulty in falling asleep; values are expressed as the number of subjects with a side effect over the total number of subjects.
^ Values are expressed as the mean ± standard deviation

Less evident were the results obtained with respect to *functio laesa*, with a reduction of approximately 25% after 6 and 10 days of treatment. In terms of tolerability, compliance and side effects, the "add-on" group showed apparently improved parameters, compared to the results obtained in group 1. Group 3 contained subjects with a new diagnosis of chronic pain (not as severe as in groups 1 and 2) that were only treated with the myrrh product (100 mg twice a day). As shown in **Table 3**, pain perception already decreased after 3 days of treatment, and was highly significantly reduced, by 50% and by more than 60%, after 6 and 10 days. In addition, *functio laesa*, a more severe parameter that is difficult to change in a short period of time, was reduced by approximately 50% after 6 and 10 days of treatment. In this group, tolerability, compliance and side effects were very good with just 2 cases of anxiety and insomnia, most likely to be nocebo effects.

Table 3 Results observed in subjects (N=26) with a new diagnosis of non-severe chronic pain administered the myrrh product at a dose of 100 mg twice a day

	T=0	T=3	T=6	T=10
Pain perception ^	4.4±0.8	2.8±0.5°	2.2±0.6°	1.4±0.2°°
Functio laesa^	3.0±0.5	2.6±0.4	1.5±0.6°	1.4±0.6°
Tolerability	good	good	good	good
Compliance	good	good	good	good
Side effects*	///	2/26	2/26	2/26

°p<0.05 versus T=0; °°p<0.01 versus T=0.

***** Main side effects reported were anxiety and difficulty in falling asleep; values are expressed as the number of subjects with a side effect over the total number of subjects.
^ Values are expressed as the mean ± standard deviation

Discussion

Our study aimed to verify the analgesic properties of RodeMyr®, a highly standardized dry myrrh extract, when administered at a dose of 100 mg twice a day as a sole or add-on therapy for subjects suffering from chronic pain.
According to the obtained results, the myrrh product demonstrated its effectiveness as an

analgesic both in already treated and naïve subjects. No significant differences were observed in terms of the age and sex of the treated subjects and similar effects were obtained when the product was administered as an add-on therapy or alone as a unique treatment. Tolerability was very good, both when the product was administered alone or as an add-on therapy.

Our study has certainly some limitations such as the low number of subjects enrolled, it was an open rather than a placebo-controlled study and only a few types of pain were considered; nevertheless, we believe that the results are a good confirmation of the analgesic effects of myrrh that have been described by many authors and give a clear contribution to our understanding of the possible medical role played by botanicals in human pathology. Moreover, this study confirms the relevant role played by a particular chemical profile and standardization process in manufacturing a myrrh-based product showing clinical efficacy in a finished product tested at 100 mg twice a day.

Conclusions

On the basis of our pilot study, RodeMyr® can be considered a safe and effective dry extract of myrrh that is endowed with analgesic effects, and Mirra+® is a useful nutritional supplement, when applied as an add-on or sole therapy, in the reduction of pain perception by subjects affected by chronic muscle, joint or back pain.

Conflict of Interest

None of the authors report a conflict of interest.

Acknowledgements

We wish to thank Professor Giovanni Appendino for acting as Editor-in-Chief for this paper.

References

1. www.escop.com

2. Wichtl M, Neubeck M (1999) Myrrhe. In: Hartke K, Hartke H, Mutschler E, Rücker G, Wichtl M (eds) Kommentar zur Europäischen Arzneibuch. Stuttgart: Wissenschaftliche Verlagsgesellschaft, 12 Lfg:M 87

3. Wiendl RM, Franz G (1994) Myrrhe – Neue Chemie einer alten Droge. Dtsch Apoth Ztg 134:25–30

4. Martinetz D, Lohs K, Janzen J (1988) Zur Chemie der Myrrhe. In: Weihrauch und Myrrhe. Kulturgeschichte und wirtschaftliche Bedeutung: Botanik, Chemie, Medizin. Stuttgart: Wissenschaftliche Verlagsgesellschaft, pp 169–180

5. Shen T, Wan W-Z, Wang X-N, Yuan HQ, Ji M, Lou HX (2009) A triterpenoid and sesquiterpenoids from the resinous exudates of Commiphora myrrha. Helv Chim Acta 92:645–652

6. Mincione E, Iavarone C (1972) Terpeni dalla Commifera mirra arabica. Nota II. Chim Ind 54:525–527

7. Dolara P, Luceri C, Ghelardini C, Monserrat C, Aiolli S, Luceri F et al. (1996) Analgesic effects of myrrh. Nature 379:29

8. Carter GT, Duong V, Ho S, Ngo KC, Greer CL, Weeks DL (2014) Side effects of commonly prescribed analgesic medications. Phys Med Rehabil Clin N Am 25:457–470

9. Shen T, Li G, Wang X, Lou H (2012) The genus Commiphora: a review of its traditional uses, phytochemistry and pharmacology. J Ethnopharmacol 142:319–330

10. Martinetz D, Lohs K, Janzen J (1989) Myrrhe als Arzneimittel. In: Weihrauch und Myrrhe. Kulturgeschichte und wirtschaftliche Bedeutung: Botanik, Chemie, Medizin. Stuttgart: Wissenschaftliche Verlagsgesellschaft, pp 141–151

11. Germano A, Occhipinti A, Barbero F, Maffei ME (2017) A pilot study on bioactive constituents and analgesic effects of MyrLiq, a Commiphora myrrha extract with a high furanodiene content. BioMed Res Int 2017:Article ID 3804356, 1–11

12. www.salute.gov.it

13. Ceccherelli F, Lovato A, Piana E, Gagliardi G, Roveri A (2012) Somatic acupuncture versus ear acupuncture in migraine therapy: a randomized, controlled, blind study. Acupunct Electrother Res 37:277–293