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## **To treat snoring with nasal steroids—effects on more than one level?**

Elisabeth Hultcrantz , Lena Harder, Henrik Harder, Eva-Lena Zetterström and Karin Roberg

### **Abstract**

**Conclusion:** An inflammatory swelling in the uvula and nose due to vibration might be one of contributing factors in snoring. Presence of corticosteroid receptors in the uvula indicates a possibility for treatment with local steroids. Three months treatment with mometasone furoate reduced snoring and related symptoms in some patients.

**Objective:** To investigate the effect and safety of a nasal steroid, mometasone furoate (MF), on snoring and related discomfort.

**Method I:** Six patients with social snoring had uvular and nasal biopsies examined using immunohistochemistry to evaluate whether corticosteroid receptors were present. **Method II:** 100 patients with snoring, not earlier using steroids, answered a questionnaire about symptoms, had ENT status assessed and used a diary for seven days reporting sleep and related variables. After randomization to placebo or MF, they used nasal spray for three months. Thereafter the same procedure was repeated. **Results:** Corticosteroid receptors were present in the mucus membranes and around the blood vessels in all uvulas. No decrease in “mean snoring score” was seen. Day-time sleepiness and stuffed nose showed a slight improvement in the MF group and the partners were less disturbed. Minor side effects were reported, equal for both groups.

### **Key Words:**

Snoring, Nasal steroids, Corticosteroids receptors, Uvular histology

**Running title:** Effects of mometasone on snoring.

## **Introduction**

Snoring is a very common symptom and an increasing problem in most societies [1-3].

The vibrations caused by air passing through a too-narrow "tube" with soft walls, will create a snoring sound due to the Bernoulli effect. The effects on the palatal muscles have been studied in snoring patients [4] where nerve degeneration seems to be the result.

The snoring sound is usually omitted by the uvula and soft palate regardless of whether the person breathes through their mouth or nose. Not only those parts but also the tonsillar pillars and the walls of the pharynx and hypopharynx are exposed to the traumatising suction force. Many patients experience become aware of the situation through feeling a soreness in the throat, especially in the mornings, as well as a lump-in-the-throat sensation because of a swollen uvula. Some show up in the clinics with an acute oedema of the uvula and may be perceived to have an infection although the more possible cause is "a hard day's night" with excessive snoring vibrations. This trauma has been noted as changes of both the epithelium and the soft tissues of the uvulas in snorers in comparisons to controls [5-6]. Magnitude of snoring is difficult to measure—the duration and the sound pressure level are only two of several variables which cause the annoyance for the patient and or for the bed partner. Questionnaires are most often used for evaluation of the patient's direct or indirect problems with snoring.

Nasal corticosteroids are commonly used for treatment of allergic rhinitis and also vasomotor rhinitis [7]. Since those conditions are quite common, they might be a contributing cause for snoring in the first place. Preventing a stuffed nose and making it possible to breath freely, might also be a good method to preventive further progress of snoring towards a sleep apnea syndrome [8]. Thus the questions arise, "Can nasal steroids have a reducing effect on snoring also by their passage through the epipharynx and pharynx? Might it be possible for the drug to

adhere to the rear side of the soft palate and uvula and thereby counteract the oedema which the nightly mechanical vibration trauma of snoring may cause?"

The purpose for the present investigation was to:

- 1) Determine whether receptors for corticosteroids are present in the uvular tissue as well as in the nose.
- 2) Study the safety and efficacy of a nasal corticosteroid, mometasone furoate (Nasonex®), on sleep related breathing disorder and related symptoms in patients with predominately social snoring.

The investigation was initiated by the researchers as a project for students in Medical School, Linköping University semester 8-11 and was approved by the Ethical Committee of Linköping University.

### ***Material and Method I***

Six patients between 40–60 years, who were operated with a modified uvulopalatopharyngoplasty including uvulectomy using RF surgery (Ellman Surgitron<sup>TM</sup>), gave their informed consent for investigation of their uvulas. Preoperative sleep registration had shown socially disruptive snoring and/or mild obstructive sleep apnea (AHI<10). To obtain positive controls for the immunohistochemical analysis, biopsies from nasal mucosa were taken in two of the cases on the same occasion.

### **Immunohistochemical Analysis**

Uvula specimens as well as biopsy specimens from nasal tissue were fixed in 4% buffered formalin for 24 hours and thereafter embedded in paraffin. The sectioned (5µm thick) uvulas and nasal biopsies were mounted on positively charged slides, deparaffinized in xylene, and rehydrated through decreasing concentrations of ethanol. Thereafter, the sections were

immersed in a pressure cooker with 10mM citrate buffer (pH 6) for 5 minutes, blocked with 5% normal goat serum and incubated for 1 hour at room temperature with rabbit polyclonal anti-mouse glucocorticoid receptor (GR) against the amino terminus of GR- $\alpha$  (Santa Cruz Biotechnology, Santa Cruz, California) at a dilution of 1:25. In a negative control, the specific polyclonal antibody was replaced with immunoglobulin fraction of nonimmune rabbit serum (Santa Cruz Biotechnology). Staining was achieved with a rabbit ImmunoCruz Staining System (Santa Cruz Biotechnology). The sections were counterstained for 1 minute with Mayer's hematoxylin and mounted with Entellan (Merck, Darmstadt, Germany).

### ***Material and Method II***

Five medical students participated in the planning of the study and the practical clinical work over the three years the inclusion and completion lasted.

100 patients between the ages of 18 and 70 years, (25% women), entered the study. They had all been referred by their general practitioner to the ENT Department of Linköping University Hospital for evaluation and treatment of snoring or sleep apnea. The study was planned to take place during the waiting period before the patients went through their sleep study—normally this would be about three months. The referrals were assessed with the aim of reaching those patients suffering from social snoring or OSA of a lesser magnitude. A letter inviting patients to participate in the study was sent to those of the right age and without any obvious factors rendering them unfit to participate. Persons with known allergic or vasomotor rhinitis were excluded as were those who were using corticosteroids for other reasons. The patients replied by mail as to whether they were willing to take part in the study.

## Baseline Visit

### Questionnaire

During the baseline visit, the patient first met one medical student taking part in the project.

The first step was to complete a questionnaire assessing their general health as well as specific issues concerning snoring and sleeping habits.

A **Snoring score** was calculated for each patient pre- and post- treatment by the means of the scores from the five questions below about different snoring-related symptoms.

0= never, 25= seldom, 50= now and then, 75= rather often, 100 = very often

1. How often do you snore?
2. How intense is your snoring?
3. How often do you sleep alone because of your snoring?
4. How often do you have short awakenings during the night?
5. How often do you wake up with a feeling of not being able to breath?

A **Sleepiness Score** was calculated for each patient pre and post treatment by the means of scores from the seven questions below about sleepiness-related symptoms.

0= never, 25= seldom, 50= now and then, 75= rather often, 100 = very often

1. How often do you not feel well rested in the morning?
2. How often do you feel sleepy during the day?
3. How often do you fall asleep during the day, when you did not mean to?
4. How often do you fall asleep in front of TV?
5. How often do you take a nap intentionally?
6. How often do you have difficulties to concentrate?
7. How often do you have difficulties with your memory?

Two questions about soreness or other discomfort in the throat at awakening were asked— “how often” and “how much”—and two questions about stuffiness of the nose—“how often” and “how much”. These were graded in the same way as above. The mean from the answers from these four questions gave a “nose and throat trouble score”. The questionnaire was in part based on an already existing instrument that had been used at the ENT Department for many years, but not been validated.

The student noted height/weight of the patient and briefly explained the study procedure for each patient. Patients with BMI  $\geq 30$  were not to be included.

Each participant was given verbal as well as written information regarding spraying technique. The participant was given a diary for him/her to fill over a period of one week to document sleep quantity, quality and whether snoring occurred for each night. Another diary was enclosed to be filled in by the spouse during that same week.

Thereafter, the participant met one of the two physicians involved, who took a complete case history and completed the ENT status. The physician made the final decision on which patients to include into the study based on the presence of any of the exclusion criteria: severe symptoms of apneas, blocked nose due to septal deviation, ongoing treatment with nasal steroids or decongestants, thereby excluding the ones with known allergic rhinitis, pregnant or breast feeding women, with any clinically significant disorder of the cardiovascular, neurologic, hematologic, gastrointestinal, cerebrovascular, immunologic or respiratory system other than asthma or COPD, or any other disorder which might interfere with the study evaluations or affect patient safety, or with a history of drug abuse or any other emotional or intellectual problems which might limit the validity of consent to partake in the study. Finally, the patient gave their written consent to participate in the study and to have their medical records monitored.

The patients were randomly allocated, 1:1, to receive either mometasone furoate (Nasonex<sup>™</sup>) or placebo. Participants were to begin spraying following completion of the pre-treatment diaries, applying a total of 200 µg of MF 50 µg/actuation or placebo each night before bedtime. MF and placebo were provided by the pharmaceutical company *Schering-Plough AB* which was at the same time responsible for the allocations.

### Starting spraying

One week after Baseline Visit, a contact with the patient was made by a student over the phone to check the completion of the diaries and to take care of any issues/questions they might have, after which the participant was allowed to commence spraying.

The nasal spray was used for a period of ninety days. In case any adverse event occurred, the participant was advised to make contact with one of the students that forwarded the message, if necessary, to the doctors. In case of nose bleeding, the participants were to stop using the spray for a couple of days and then resume—initially at a lower dose.

Approximately two and a half months into the treatment period, each participant was contacted by a student to schedule a final visit. Another set of diaries was sent by mail to be filled in by the participant and partner during the final week of treatment. Also enclosed was questionnaire # 2, which in addition to the questions in questionnaire # 1, had questions regarding how the patients themselves had experienced the treatment.

### Final Visit

The participants returned any left over medication as well as the diaries and questionnaire.

The medications were subsequently taken care of by the hospital pharmacy. Post-treatment weight was noted and a physical examination of the ENT status was performed. The patients were also asked to relate how they had experienced the treatment and its effects/side effects.

A sleep study was scheduled as soon as possible after the Final Visit, but those results were not part of this investigation.



## Statistical analysis

A descriptive analysis was performed for the histochemical part of the study.

The primary efficacy variable to analyse in the clinical trial, was the difference between the “mean snoring score” for the two groups (MF treated and Placebo) based on the answers in the questionnaires completed at baseline and after ninety days. Secondary efficacy variables were the difference in mean “sleepiness score”, similarly calculated for each group; MF-treated and placebo-treated and also for the “nose; and throat trouble score” . The groups were compared as to differences from pre-treatment to post-treatment using a two-sample t-test or if, the data distribution called for it, with Wilcoxon-Mann-Whitney’s 2-sample test. The exploratory analyses of each single question was done using a two-sample  $\chi^2$  tests. Statistical sign level will be 0.05. Using the same methods, the groups were also compared with respect to Epworths Sleepiness Scale (ESS) and each question in the diaries. A power of 90% was calculated assuming a difference between the groups after treatment with two steps regarding reduction of mean snoring score.

## **Results**

### I. Immunohistochemical analysis of glucocorticoid receptors

In the positive control from nasal tissue, GR labelling was localized in the cytoplasm and nucleus of the surface mucosa, submucosal glands, endothelial cells and inflammatory cells.

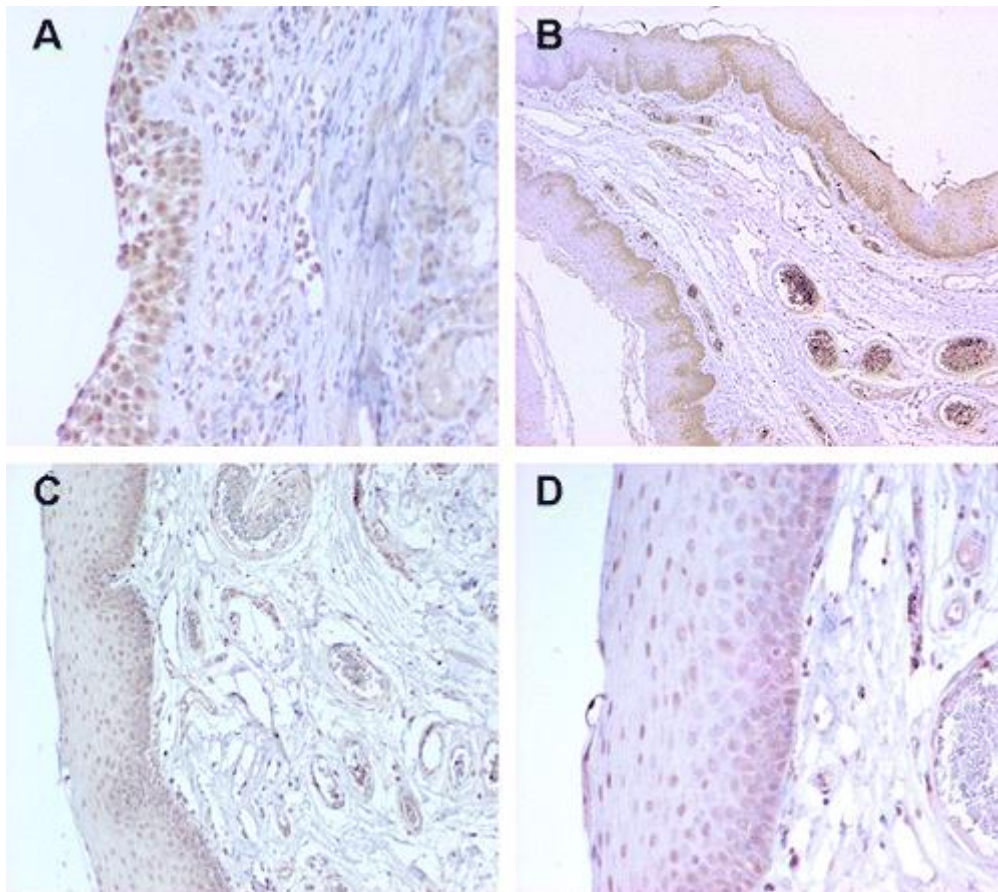
In the negative control, no GR labelling was found. In uvulas from patients with social snoring, GR labelling was observed in all examined tissue specimens. The labelling was localized mostly in the nucleus of the surface mucosa, in endothelial cells around the blood vessels and in inflammatory cells (Figure 1A, B and C).

### II. Clinical trial

Five medical students got scientific training within the project. Two wrote about “Good Clinical Practice”, another two discussed the results: ”Can Nasonex help against snoring?”

and the last one made a comparison between the results from the questionnaires and the diaries in relation to the results from the later performed sleep registration: “ How to evaluate snoring and its consequences- A comparison between three different methods”.

84 out of 100 enrolled patients followed the study per protocol. 64 of them had also a partner who had completed the diary and questionnaires.



*Figure 1. Immunohistochemical staining for the glucocorticoid receptor (GR) on cross-sections of the uvula (A and B). GR immunoreactivity in cell nuclei is brown and nuclei without GR immunoreactivity remain blue. (C, D) Positive control from nasal biopsy.*

Ten patients, 7 men and 3 women, did not complete the treatment. Two of them (MF) stopped spraying as they felt no improvement and had trouble remembering to use the spray regularly. Two became pregnant and never started the treatment. Two (1 MF and 1 Placebo) experienced side effects and chose to discontinue. Fear of side effects led one man (MF) to drop out. One man did not disclose the reason for his dropout. The last woman (MF) to drop out moved out of the country, and thus was lost to follow-up.

Six participants did not complete questionnaire #2 and thus were excluded from the analysis.

*Table 1. Changes in mean score for snoring, sleepiness and nose-throat discomfort after three months of treatment with MF or placebo.*

	<b>Treatment</b>	<b>Change</b>		<b>Stat.</b>
Snoring score (0-100)	MF	38	-4,4	n.s.
	Placebo	45	-1,6	
Sleepiness score	MF	38	-2,5	n.s.
	Placebo	45	-2,1	
Nose-throat discomfort score	MF	37	-4,8	n.s.
	Placebo	45	-4,9	
Epworth sleepiness Scale (0-24)	MF	37	-1,0	n.s.
	Placebo	42	-0,7	

## Efficacy

The variables analyzed were defined and categorized to values between 0, 25, 50, 75 and 100, higher values representing more advanced symptoms. Six out of 38 MF patients and one out of 45 placebo patient improved by 2-3 steps on the snoring score . The results from the questionnaires calculated for the whole group are presented in Table 1. The resulting mean “snoring score” for the whole MF group was 60 before and 55 after treatment. For the placebo group, the corresponding values were 55.5 and 55.1. These differences are not significant.

The change of “sleepiness score” was 2.5 units in the MF group and 2.1 in the placebo group.

Both groups reduced their ESS score by 1 unit.

Comparison of the answers in the diaries, based on seven nights’ observation demonstrated differences between the MF and the placebo group with respect to the feeling of “being rested in the morning” ( $p < 0.015$ ) where the MF group had improved and in “stuffed nose in the morning” ( $p < 0.021$ ) with a slight worsening of the MF group, (Table 2). The partner’s sleep was improved during the time the snorer used MF ( $p < 0,01$ ). (Table 3). The change in throat discomfort in the MF group was 7.3 units and in 4.0 the placebo group. (ns)

Analyzing the degree of blockage in the nose gave the results that the MF group had improved 5.1 units and the placebo group 4.1.

## Adverse effects

A total of 19 participants reported adverse effects— 21 % of the study population. Ten of these had been allocated to MF. The complains, which were of little significance to the patient, varied from feeling of dryness of the mouth relieved by drinking water, to a feeling of discomfort in the nose after spraying. Neither of these effects was reported to affect compliance. A few experienced epistaxis or blood tinged mucous on one or more occasions which ceased in a few minutes time. Some patients experienced more than one side effect.

Table 2. Effect of MF or placebo on daily recorded symptoms.

Means from patient diaries, seven days pre- respectively post treatment and change of symptom scores (pre= pre-treatment, post=post treatment, change= change in score, stat.= statistic significance)

	Treatment	Pre		Post		Change		Stat.
		n		n		n		
Did you snore during the night? <i>1=yes, 2=no</i>	MF	31	1,041	29	1,056	26	-0,052	n.s.
	Placebo	36	1,05	29	1,066	26	-0,04	
How well rested did you feel this morning? <i>1= very tired - 4= well rested</i>	MF	36	2,297	36	2,542	34	-0,282	p=0,015
	Placebo	44	2,424	41	2,463	40	0,002	
How many times did you wake up during the night? <i>No. times</i>	MF	35	2,455	34	2,106	32	0,406	n.s.
	Placebo	40	2,426	36	2,19	33	0,252	
For how long did you sleep during the night? <i>Minutes</i>	MF	36	414,2	36	416	34	-5,7	n.s.
	Placebo	45	427,4	41	442,9	41	-17,7	
What degree of throat discomfort did you experience this morning? <i>1=none -4= severe</i>	MF	35	1,527	36	1,645	33	-0,184	n.s.
	Placebo	45	1,59	41	1,686	41	-0,094	
What degree of stuffed nose did you experience this morning? <i>1=none - 4= severe</i>	MF	35	1,406	36	1,558	34	-0,202	p=0,021
	Placebo	45	1,521	41	1,557	41	0,01	

## Discussion

This study has suggested that uvula might have a similar content and distribution of GRs as nasal tissue. After immunohistochemical analysis, we could demonstrate that GRs were present in uvulas from patients with socially disruptive snoring or mild obstructive sleep apnea syndrome. These results were a prerequisite for the hypothesis that nasal steroids (mometasone furoate) might have a positive effect on snoring and its related symptoms. GRs, which belong to the superfamily of nuclear hormone receptors, mediate most of known effects of glucocorticoids [9]. The glucocorticoid affinity sites in nasal tissue have been shown to be in epithelium, veins, leukocytes, and glands [10] and we could now see the same distribution in the uvular tissue.

Table III. Effect of MF or placebo on daily recorded symptoms

		Pre		Post		Change	Stat.	
	Treatment	n		n		n		
How did you sleep during the night? <i>1=not at all - 5= very well</i>	MF	33	3,565	29	3,761	29	-0,201	p=0,01
	Placebo	42	3,798	33	3,732	33	0,164	
Did your partner's snoring wake you up? <i>1=yes, 2= no</i>	MF	33	1,304	28	1,381	28	-0,108	n.s.
	Placebo	42	1,385	33	1,438	33	0,008	
How many times did your partner's snoring wake you up? <i>No. times</i>	MF	31	2,94	28	3,526	27	0,646	n.s.
	Placebo	37	2,849	27	1,245	25	0,299	

In this study, a decrease in the severity of snoring was noted among a few patients treated with MF, indicating a possible future role for some patients for this line of treatment. In recent years there have been studies suggesting that nasal steroids might have a role in treating paediatric obstructive sleep apnea due to adenotonsillar hypertrophy [11]. There is also support for treating adults with sleep apnea and rhinitis where a reduction of AHI could be seen although without effect on the snoring sound [8]. Since all results in this study were based on a small population, a minor difference between the MF and placebo group will not always show a statistical significance. A larger population has to be studied in order to draw reliable conclusions. The power calculation performed when the study was planned was too optimistic about the expected effects.

There was a slight increase of the score for blocked nose in the MF group, which was not expected. Considering the fact that allergic/vasomotor rhinitis is already an indication for this drug [5], one could have thought that at least some patients would experience improvement from the spray due to a previously undiagnosed nightly chronic nasal congestion based on allergic or vasomotor rhinitis not noticeable at the clinical examination in daytime. A possible link of snoring to allergic or vasomotor rhinitis would be of interest to explore further. Regardless of cause, chronic nasal congestion in itself has been identified as a risk factor for snoring and OSA [12-13]. The fact that snoring patients often experience

discomfort and/or soreness of the throat is a common clinical finding, not yet fully investigated. One contribution may be reflux of sour content from the ventricle [17].

Evidence of inflammatory changes in the oropharyngeal mucosa of the snoring patients [14-15] led to our new hypothesis that steroid treatment might be useful. The patients included in the trial had all relatively mild symptoms and signs to start with, and no visible change in the condition of their throats was noted after the treatment. However, better sleep was noted for both the patient and the partner which might be an indirect sign of a therapeutic effect.

For ethical reasons, it was not possible for the more severely affected patients—who might have demonstrated more clinical signs—to wait the three months taken by this study before they were given their sleep studies. However, since snoring is a significant social and domestic problem and is closely related to OSA, it carries with it profound morbidity and negative impact on the quality of life for those who suffer from it. Thus, any new therapeutic strategy aimed at this illness is of importance.

It is not to be expected that nasal steroids will cure patients who are also suffering from OSA, because the primary locus for the apneas is in the hypopharynx [16]. If daytime sleepiness is related to the apneas and not to the snoring sound/ breathing effort, a large decrease of mean sleepiness score would not be expected.

Following intranasal delivery of steroids, a large proportion of the drug is swallowed due to mucociliary clearance from the nose to the throat [18]. We propose that some of the drug can remain in the oropharyngeal region thereby rendering beneficial, anti-inflammatory effects on tissues damaged by snoring. The presence of steroid receptors in this area was clearly demonstrated, supporting our hypothesis. It is not impossible that the slight reduction of snoring noted in some patients of this study in part produced by this effect of nasal steroids on the soft palate.

That both groups experienced adverse effects of the same kind and degree, suggests that the side effects are not only due to the MF, but could just as well be caused by other ingredients in the formula. The side effects of MF reported in the present study do not differ from those documented in previous studies using MF nasal spray [19]. Systemic effects such as suppression of the HPA axis have been excluded at the dosage of 200 micrograms a day in several studies [18]. However, these findings are not uncontroversial [10].

Generally, the participants reported no difficulties in using the spray. However, it was noticed that the amount of spray used varied quite considerably judged by the differences in the amount of medicine returned on the second visit. The reason for this may be lack of compliance (i.e., they had not used the spray as often as instructed), or that they used an inadequate technique. Thus, the actual amount of spray consumed, reaching the target area (the soft palate) may have varied. This could have had the effect that some patients did not achieve the therapeutic window of the drug, leaving little hope of effect. This problem could have been further assessed/quantified by measuring the weight of the returned spray.

Further studies assessing the effectiveness of topical steroids are necessary, not only in establishing an effect but also to distinguish those patients who might benefit from treatment. Also left to be determined are how long the treatment should last if it is to produce the desired effect, and, if spraying is discontinued, how long does the effect persist?

The medical students working in the project got a clear view regarding much time and work is required by every step in clinical science and how new questions arise during the process. They all got good experience in handling the patients which will be useful for their further medical careers.

## Conclusion

Receptors for corticosteroids are available in the uvular tissue as well as in the nasal mucosa, thus nasal steroids may have an effect on reducing the development of vibration related oedema and snoring. This could be achieved not only by effects in the nose, but also by



influence on the swelling of the soft palate caused by vibrations of the tissues. For the few patients who react positively, the treatment with intranasal steroids is a user-friendly and safe method compared to other tested drugs [20].

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