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Preclinical and Clinical Overview of Terpenes in the Treatment of Urolithiasis

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Article info

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Abstract

Context: Pharmaceutical support for spontaneous stone expulsion therapy or fragment clearance after shock wave lithotripsy (SWL) is standard of care in the daily urologic routine. Besides tamsulosin and calcium-channel antagonists, biological products such as terpen combinations are suggested as promoters of stone expulsion.
Objective: To summarize the literature on terpen combinations in the pharmaceutical treatment of urolithiasis.
Evidence acquisition: The manuscript is based on a presentation given at a symposium on "Terpenes in urolithiasis" that was held in Düsseldorf, Germany, in 2010. Data were retrieved from critically selected publications.
Evidence synthesis: Rowatinex is a combination of seven naturally available terpenes. The pharmaceutical effects of the included terpenes are diuretic, spasmolytic, antibacterial, and hyperemic. Consequently, Rowatinex is considered a valuable medication in the treatment of urolithiasis. Despite a long history of clinical availability for Rowatinex, with >50 yr since product placement, the number of available publications is straightforward; however, four open controlled and five prospective randomized trials are published. The majority of these publications show favorable results for Rowatinex compared with placebo in terms of stone expulsion rate and fragment expulsion after SWL. Rowatinex seems to have a good safety profile, with a low incidence of adverse events, which are mainly of gastroenterologic nature.
Conclusions: As a combination of seven naturally available terpenes, Rowatinex seems to have the potential to promote and accelerate stone expulsion in primary management of urolithiasis as well as fragment discharge after SWL. In doing so, Rowatinex shows superior results over placebo in the majority of the published studies. Large-scale randomized trials comparing the effect of Rowatinex versus tamsulosin and calcium-channel antagonists are pending.

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1. Introduction

Watchful waiting therapy to obtain spontaneous stone passage, either following shock wave lithotripsy (SWL) or as primary treatment, is an accepted treatment option for patients with controlled symptoms and nonimpaired renal function and without signs of infection. Accompanying this treatment strategy with pharmacologic medical expulsive therapy may improve stone-free rates and symptoms during stone passage. In particular, α-adrenergic blocking

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agents and calcium-channel antagonists have proven efficacy in randomized controlled studies [1–7]. Additional combination with nonsteroidal anti-inflammatory drugs, steroids, and spasmolytics may further improve stone passage [1,3,8]. Terpen combinations derived from naturally occurring essential oils have been suggested to improve stone-free rates and symptoms during stone passage in patients with urolithiasis [9–13]. This paper summarizes the published literature on terpen combinations in the treatment of urolithiasis.

2. Evidence acquisition

This paper was based on a presentation given at a symposium on "Terpenes in urolithiasis" that was held September 21, 2010, in Düsseldorf, Germany. Data were retrieved from critically selected publications.

3. Evidence synthesis

3.1. Terpenes

Terpenes are constituents of essential oils and are prevalent in many plants. In general, terpenes represent a heterogeneous group of chemical substances constructed from hydrocarbons. Variation in additional chemical compounds, such as alcohols, aldehydes, or ketones (terpenoids), define the variations of the different terpen composites.

The building block of all terpenes is the hydrocarbon isoprene (C_5H_8), and classification is achieved according to the number of isoprene units (eg, monoterpenes, carrying two isoprene units). Despite other effects, terpenes are known to have diuretic and antibacterial effects as well as spasmolytic and hyperemic effects. Consequently, terpenes may have the potential for use in the medical treatment of urinary tract pathologies, such as stone disease.

3.2. Pharmacologic background of terpen combinations in the treatment of urolithiasis

Rowatinex (ROWA Pharmaceuticals Ltd., Bantry, Co. Cork, Ireland) is a medical product containing a combination of seven naturally occurring terpenes (31% pinene, 15% camphene, 10% borneol, 4% anethole, 4% fenchone, and 3% cineole). Due to the pharmacologic effects of these terpenes, Rowatinex is thought to have beneficial effects on conservative stone management and to support medical expulsive therapy.

The pharmacologic effects of Rowatinex are defined through the single terpenes used in this formulation (Table 1). Antibacterial effects of Rowatinex were described by Cipriani and co-workers [14], with pinenes being the most potent antibacterial substance, followed by borneol and fenchone.

Various groups showed spasmolytic activity of terpenes in multiple animal model studies. Spasmolytic activity (intestinal segments) was proven in guinea pigs, rabbits (also with aortic segments), and cats [15–17]. In addition, hyperemic action could be demonstrated by Geinitz [18] and by Stern and Vukcevic [17] as early as 1956 and 1960, respectively.

Table 1 – Pharmacologic effects of terpenes

Terpenes	Pharmacologic effect
Pinene	Diuretic, antibacterial
Camphene	Hyperemic, choleretic, antibacterial, spasmolytic
Borneol	Choleretic, vasodilatory, antibacterial, analgesic, spasmolytic
Anethol	Diuretic, anti-inflammatory, antibacterial, choleretic, hyperemic
Cineole	Antibacterial, spasmolytic
Fenchone	Antibacterial.

Because terpenes are lipid-soluble substances, the components of Rowatinex are rapidly absorbed after oral intake and are metabolized and excreted mainly with the urine and only to a minor extent with the feces. Rodent studies for pinenes have indicated that hydrocarbons in this chemical category participate in similar pathways of absorption, metabolism to polar oxygenated metabolites, and excretion [19]. Terpen absorption and excretion was also investigated by Kohlert et al. [20]. The authors were able to demonstrate rapid increase of terpen plasma levels in pinenes, camphor, and limonene after dermal application in human subjects, whereas the majority of metabolites were excreted with the urine.

Due to the described pharmacologic effects, terpenes were considered to have potential use in urinary tract pathology, especially in urolithiasis. Rowatinex was introduced in Europe in 1954, and since then, it has been launched in >60 countries worldwide. According to the sales volume given by the manufacturer, an average of 1.5 Mio capsules of Rowatinex are administered per year, showing the broad distribution of the substance.

3.3. Rowatinex in the treatment of urolithiasis

Despite the long history of Rowatinex being introduced in the conservative treatment of urolithiasis, the number of published studies is manageable. In addition, a fair number of case reports have been published, including data from 1095 patients. However, due to the nature of these case reports (varying dosage and formulations as well as indications) and the limited possibility of comparing these results, case reports are omitted from further analysis in this overview. In the following sections, open controlled ($n = 4$) and prospective randomized ($n = 5$) trials are summarized to characterize the effects of Rowatinex in the treatment of urinary stone disease.

3.4. Open controlled studies

In 1959, Asai et al. [21] published an early report summing up their results of 24 patients treated with Rowatinex for urolithiasis. The authors report spontaneous stone passage in 14 of 24 patients (58.3%) and improvement in patients' symptoms in 21 of 24 subjects (87.5%). Within 2 wk of treatment initiation, 9 of 14 patients with stone passage

Table 2 – Overview of prospective randomized trials

	Primary end point	Group of randomization	No. of patients (male: female)	Age, yr	Stone diameter, mm	Treatment duration, days, *n* (range)	Success rate, *n* (%)		Side effects
Mukamel et al. [10]	Stone expulsion rate in ureteric calculi	Rowatinex	23 (20:3)	45 (26–74)	5.2 (1–12)	10.8 (1–21)	18/23 (78)		*n* = 6 (mild nausea)
		Placebo	17 (12:5)	40 (20–53)	2.5 (1–7)	11.7 (2–21)	9/17 (52)		None
Engelstein et al. [9]	Stone expulsion rate in ureteric calculi	Rowatinex	43 (38:5)	44 (26–74)	4.0 (1–12)	Approximately 14 (NR)	35/43 (81)		*n* = 7 (mild nausea)
		Placebo	44 (34:10)	48 (26–75)	2.6 (0.5–7)	Approximately 14 (NR)	26/44 (59)		None
Aldemir et al. [24]	Stone expulsion rate in distal ureteric calculi <10 mm	Rowatinex	30 (17:13)	46.5 (22–76)	6.8 (3–10)	6 (NR)	13/30 (43.3)		None
		Tamsulosin	31 (22:9)	42.2 (22–75)	6.7 (4–10)	3.5 (NR)	25/31 (80.6)		None
		Diclofenac	29 (19:10)	43.5 (18–71)	6.6 (4–10)	7 (NR)	11/29 (37.9)		None
Djaladat et al. [25]	Fragment expulsion rate after SWL	Rowatinex	50 (30:20)	38.3 ± 16.4	NR (10–20)	28 (NR)	Day 14	Day 28	None
							9/50 (18)	12/50 (24)	
		Placebo	50 (29:21)	40.9 ± 14	NR (10–20)	28 (NR)	2/50 (4)	9/50 (18)	None
Romics et al. [26]	Fragment expulsion rate after SWL	Rowatinex	106 (62:44)	51 (18–82)	6.5–7.0 (2–19)	98 (NR)	53/66 (80.3)*		*n* = 7 (diarrhea [3x], headache, vertigo, nausea, vomiting)
		Placebo	98 (53:45)	48 (18–78)	6.5–8.0 (3–20)	98 (NR)	41/74 (55.4)*		*n* = 2 (diarrhea)

NR = not reported; SWL = shock wave lithotripsy.
* Patients with complete 98-d follow-up.

expelled their stone and an additional 12 patients were reported to have significant stone migration. All discharged calculi were <0.9 cm. The authors conclude that Rowatinex may be an effective support of medical expulse therapy. In 1961, Hammer and Rothe [22] published a report on 50 patients treated with Rowatinex for radiologically proven calculi in the distal ureter or renal pelvis. Treatment duration in all patients exceeded 6 mo and led to spontaneous stone passage in 37 of 50 patients (74%). Furthermore, 43 patients (86%) reported improvement of their symptoms.

Siller et al. [23] were the first to evaluate the effect of Rowatinex on stone-free rates in patients who received SWL. In their study, 50 patients (28 men and 22 women) were treated with Rowatinex capsules after uncomplicated SWL of renal and ureteral calculi. Treatment was accompanied by increased fluid intake to ensure a daily urine volume of >2.5 l. Inclusion criteria in this study were stone size <20 mm without obstruction of the urinary tract and without the history of deobstructing interventions such as DJ-Stent placement or nephrostomy tube. All patients received Rowatinex capsules (three times per day) for 28 d following SWL and were followed up at days 1, 14, and 28 post-treatment. Pretreatment stone location was renal pelvis and calices in 89.2% of the cases and upper and middle section of the ureter in 10.8%. The stones were <10 mm in 86%, and the remainder were between 10 and 20 mm in size. All patients received one single session of SWL, with an average of 1841 shocks (range: 1000–3000). According to the authors, 84% of the patients started to pass stone fragments on day 1 post-treatment. Overall, 60% of the patients were stone free on day 14 and 82% of the patients were considered stone free at day 28. Of the remaining patients with residual stones, eight patients showed stone fragments <5 mm, mainly located in the lower and middle calyx, and one patient had a residual stone >5 mm in the middle calyx. In addition, the authors looked at symptoms, particularly pain reduction as measured by visual analog scale, and could show symptom reduction, with a total of 94% of patients pain free at day 28 postintervention.

3.5. *Prospective-randomized trials: Rowatinex in ureteric stone expulsion*

Five randomized controlled trials have been carried out to investigate the efficacy of Rowatinex in supporting spontaneous stone passage as the primary treatment option or following SWL (Table 2).

Mukamel et al. [10] were the first, in 1987, to investigate the effects of Rowatinex on spontaneous stone passage in a prospective randomized double-blind study. Forty patients who were referred to the authors' center with acute renal colic and definite evidence of ureteric stones were included in the study. After randomization, the patients were followed for stone expulsion. The authors could demonstrate significantly higher rates of treatment success within 3 wk of treatment in the Rowatinex group compared to placebo (78% vs 52%), despite a larger stone diameter in the Rowatinex group (5.2 vs 2.5 mm). Comparing patients with

stones ≥3 mm, the expulsion rates were 61% versus 28% in favor of the Rowatinex group.

In 1992, Engelstein and co-workers presented a confirmative study on the above-mentioned investigation [9]. They included 87 patients in this observation and randomized them into a placebo group and a Rowatinex group. Again, the mean stone diameter was larger in the Rowatinex group (4 mm vs 2.6 mm). Supporting the earlier results, Engelstein et al could demonstrate significant higher rates of stone expulsion in the Rowatinex group (81% vs 59%, $p < 0.05$). Engelstein et al also reported data on adverse reaction, showing good tolerability of Rowatinex, with a total of seven patients experiencing mild nausea or abdominal pain.

Reference-controlled results were presented by Aldemir et al. [24]. Ninety patients with distal ureteral <10 mm stones were randomized into three groups, comparing efficacy and spontaneous stone expulsion rate among tamsulosin, Rowatinex, and diclofenac. With comparable demographic data and stone size in all three groups, the stone expulsion rate was significantly higher in the tamsulosin group compared to Rowatinex and/or diclofenac (80.6% vs 43.3% vs 37.9%, $p = 0.002$ and $p = 0.001$, respectively). In addition, the mean time to stone expulsion was shorter in the tamsulosin group and the need for additional analgesic drugs was reduced. No significant difference was detected in terms of the incidence of renal or ureteral colic among the three groups.

3.6. *Rowatinex following shock wave lithotripsy*

Two prospective randomized controlled trials investigate the effect of Rowatinex on stone passage and stone-free rates after SWL. In 2009, Djaladat et al. [25] reported a series of 100 patients after uncomplicated SWL who were randomized into a Rowatinex group and a placebo group. All patients were treated because of renal calculi between 10 and 20 mm in size. Patients had been followed for stone expulsion at intervals after 14 and 28 d. Although the overall stone-free rate was comparable between both groups after 28 d, the patients who received Rowatinex seemed to demonstrate accelerated stone passage. After 2 wk, only 4% of the patients in the control group were considered stone free, whereas 18% of the Rowatinex group had passed their fragments completely ($p = 0.02$). The authors concluded that despite missing advantages in overall stone-free status after 4 wk, the treatment with Rowatinex may lead to accelerated stone expulsion.

Recently, Romics et al. [26] published a prospective randomized trial of >200 patients receiving SWL and postoperative expulsion supportive therapy with either Rowatinex or placebo. This group found significantly higher rates of stone-free patients in the Rowatinex group within a 12-wk interval. Complications and adverse events were comparable in both groups.

4. Conclusions

Rowatinex is a combination of seven naturally appearing essential oils (terpenes). Due to the pharmacologic nature of the utilized terpenes, Rowatinex is used as a supportive drug in conservative stone management and stone expulsive therapy. Despite market introduction as early as 1954, only a small number of studies on efficacy and tolerability exist. Most of the reports published on Rowatinex efficacy are case reports and, due to varying indications, are hardly comparable. A total of five randomized controlled trials have been published within the last 23 yr. Four of these trials show superiority of Rowatinex-treated patients over placebo in terms of stone-free rates in conservative stone management or stone expulsive therapy following SWL, in combination with good tolerability. Especially following SWL, Rowatinex seems to provide faster and more efficient stone expulsion. However, large-scale trials comparing Rowatinex not only to placebo but to alternative pharmacologic promoters of stone expulsion (eg, tamsulosin) are missing.

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Conflict of interest

The author has received consultancy or lecturer honoraria from Rowa Pharmaceuticals.

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