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OPEN JOURNAL OF
Pharmacology and Pharmacotherapeutics
OPEN ACCESS JOURNAL

DOI: https://dx.doi.org/10.17352/ojpp

Review Article

On the anticancer clinical activity of perillyl alcohol and limonene: A critical assessment of the outcomes

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Received: 30 July, 2022
Accepted: 22 August, 2022
Published: 23 August, 2022

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Keywords: Perillyl alcohol; Clinical trials; Cancer; Glioblastoma multiforme

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Abstract

Monoterpenes with p-menthane structure (perillyl series) can inhibit Ras-proteins prenylation involved in carcinogenesis processes. To evaluate the safety and efficacy of perillyl alcohol (POH) and limonene to treat any type of human cancer, we conducted a systematic review of clinical studies found in seven biomedical bibliographic databases and four clinical trial registries. After screening titles, abstracts, and full texts for inclusion/exclusion criteria, one study on limonene (oral) and 19 on POH administered by oral (13), dermal (2), or intranasal-instillation routes (4), comprising phase I or I/II trials, were included in the review. The quality of included studies was assessed as well. No randomized and controlled phase-III trial was performed or is in progress. A critical appraisal of study results suggested that both compounds are safe after oral ingestion, dermal application, or nasal instillation. Overall, phase II studies showed no evidence of anticancer activity. Nasal instillation of POH, however, apparently prolonged the overall survival of patients with glioblastoma. Randomized and controlled (phase III) clinical studies are necessary to confirm these findings.

Abbreviations

AE: Adverse Events; CA: Carcinoma; CS: Case Series; CT: Controlled Trial; DE: Dose Escalation Design; DHPA: Dihydroperillic Acid; DLT: Dose Limiting Toxicity; FPR: Freedom from Progression Rate; GBM: Glioblastoma Multiforme; GI: Gastrointestinal; HV: Healthy Volunteers; KD: Ketogenic Diet; MTD: Maximum Tolerated Dose; OS: Overall Survival; PA: Perillic Acid; PD: Progressive Disease; PFS: Progression Free Survival; PK: Pharmacokinetic Data; POH: Perillyl Alcohol; PR: Partial Response; QID: Four Times Daily; RCT: Randomized Controlled Trial; SA: Sarcoma; SR: Safety and Apparent Response; TID: Three Times Daily; TTP: Time to Progression

Introduction

Perillyl alcohol (POH) is a monoterpene of a series of perillic compounds derived from the oxidation of the exocyclic methyl group of the p-menthane-type structure represented by limonene. The ability of perillic monoterpenoids to inhibit the oncogenic cell growth and differentiation involves either blocking the isoprenylation of Ras and Ras-related proteins [1-3] or hampering their transfer from the cytosol to the plasma membranes [4]. In particular, POH has attracted great interest because it acts on multiple cellular targets related to the cell cycle machinery and growth-regulatory processes, such as the suppression of small G proteins and 3-hydroxy-3-methylglutaryl coenzyme A reductase, whose activities are elevated in tumors [5]. Research on this anticancer compound led it to eventually become an NSC (National Spectrum Consortium)-sponsored prototypic molecule for preclinical testing, formulation, and phase I and II clinical evaluation [6,7].

The anticancer clinical effect of POH was the subject of an early systematic review on a search thereof broadened to

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limonene and other perillic derivatives [8]. In addition, a review focused on the specific effects of POH was recently reported [9]. Both systematic reviews complied with PRISMA guidelines and checklist and, after application of inclusion and exclusion criteria, ended up with the inclusion of 19 and 13 clinical trials, respectively. In both cases, the marked heterogeneity of study designs precluded any meta-analysis. The present study has a broader focus including limonene in addition to the perillic derivatives and analyzed in detail the outcomes of the clinical studies with both compounds.

Methods

Selected clinical trials

POH and limonene were the only two compounds that emerged from a systematic search in seven biomedical literature and four clinical trials databases [8]. The review followed the Preferred Reported Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist and the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0) [10]. It is registered with the *International Prospective Register of Systematic Reviews* (PROSPERO) under number CRD42018082207. The PICO framework [11]. was adopted for the eligibility criteria, as to answer the question: *What is the evidence in humans that limonene, perillyl alcohol, perillic acid, and perillaldehyde are effective and safe treatments for cancer (of any type) and precancerous lesions?* The exclusion criteria comprised conference abstracts, case reports; systematic reviews; studies on the use of any perillic derivative in combination with other drugs, cost-effectiveness studies, studies in animals, *in vitro* and *ex vivo* studies, and PK studies in healthy volunteers.

The review was first summarized on Fev-01-2018 (and further updated on Feb-28-2021) and the search found a sole study of limonene that was eligible for review. For POH, nineteen trials were included in the review [number of studies]: oral administration [13], dermal application [02], and intranasal instillation [04], comprising phase I and phase I/II designs. Data extracted from the selected studies were the number of participants, type of cancer, tested drug, study design (randomized controlled trials (RCT), nonrandomized controlled, or nonrandomized uncontrolled/single-arm, phase I, II, or III trial), comparator if used, duration of the study, safety (side effects, drug-related symptoms) and efficacy outcomes, results, administered doses, and dose regimens, and kinetic data in patients if provided. The qualitative (narrative) synthesis of the evidence provided an answer to the research question. Because nearly all phase I and II trials had no control groups, quantitative synthesis was not feasible.

Quality assessment

The Cochrane Collaboration's tool for assessing the risk of bias (RoB), was graded as high, low, or unclear, for randomized interventions [10,12] Nonrandomized uncontrolled trials (*e.g.*, case series and case reports) were assessed by the tool proposed by Murad, et al. [13]. A checklist, comprising 15 criteria, proposed by Zohar, et al. (2008) [14] was used to assess the methodological quality of phase-I cancer trials.

Results

Neither POH randomized controlled (phase III) studies were found in the searched databases, nor were protocols of POH RCTs identified in clinical trial registers [8]. The clinical trials of d-limonene and POH included in this review, with routes of administration, study design, numbers of participants, and types of malignancies treated are listed in Table 1. The adverse events and maximum tolerated doses (MTD) found in phase I trials of limonene and POH are shown in Table 2. The outcomes (safety and efficacy endpoints) of phase II studies of limonene and POH are in Table 3.

The results of quality assessment (QA) of phase I trials listed in Table 1 indicated that, except for one study [15], studies of oral limonene [16] and POH [17-22] fulfilled most of Zohar's criteria for assessing the quality of phase I trials. The studies of topical (dermal) [23] and intranasal [24,25] POH, however, failed to achieve most criteria for QA of the cancer phase I trials (data not shown). Results of the QA of phase II trials and assessments of risk of bias for limonene and POH treatments are shown in Table 4. Except for an RCT of topical POH [26], all studies were single-arm trials [7,16,27-29], or case-series of treated patients compared with a disease historical control group [30]. Owing to their methodological drawbacks (causality domain), these uncontrolled and nonrandomized phase II studies provided only limited evidence about the efficacy of POH and limonene as anticancer agents. Major limitations of the RCT dermal POH trial [26] were its high risk of selection and performance biases.

Outcomes analysis: d-limonene

A phase I trial assessed the toxicity, maximum tolerated dose (MTD), and PK of *d*-limonene in 32 cancer patients with refractory solid tumors (99 courses of *d*-limonene 500 to 1200 mg/m^2 per day administered orally in 21-day cycles). Nausea, vomiting, and diarrhea were the most frequently noted side effects, and the MTD was 8000 mg/m^2 of *d*-limonene per day [16]. One breast cancer patient showed a partial clinical response (8000 mg/m^2 per day) maintained for 11 months, while three patients with colorectal carcinoma had prolonged stable diseases. Since these findings were from a single-arm phase I trial, it is unclear whether the disease stabilization was due to treatment with limonene. A subsequent phase II trial conducted with additional 10 breast cancer patients (15 cycles of 8000 mg/m^2 per day) showed no apparent response to treatment with *d*-limonene. The parent compound and five major metabolites, including PA, a putative isomer of PA, DHPA, limonene-1,2-diol, and uroterpenol, were detected in the plasma of treated patients. PA and DHPA were also found in the patient's urine (Table 3). In summary, one study showed that patients with several types of solid tumors refractory to treatment tolerated high doses of limonene given by the oral route. No sign of clinical benefit, however, was noted in 10 breast cancer patients treated orally with limonene in a limited phase II trial.

Outcomes analysis: Perillyl alcohol administered by the oral route

Nine single-arm trials involving a limited number of

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Table 1: Clinical trials included in the review: drug,route of administration, study design, comparators, number of participants and types of cancer.

Study	Author / year	Drug/route	Design	Comparator	Participants	
					N	Cancer type
1	Vigushin, et al. 1998 [16]	d-Limonene/oral	Phase 1	No	32	Solid tumors: breast [16], colon/rectum [7], stomach [2] and other sites [7].
2	Vigushin, et al. 1998 [16]	d-Limonene/oral	Phase 2 (UC, SR, PK)	No	10	Breast cancer.
3	Ripple, et al. 1998 [17]	POH/ oral	Phase 1 (DE, PK)	No	18	Cancer (advanced): prostate [4], ovary [3], sarcoma [3], renal cell [3], breast [2], other sites [3].
4	Ripple, et al. 2000 [18]	POH/ oral	Phase 1 (DE, PK, SR)	No	16	Cancer (refractory advanced): prostate [4], ovary [3], colorectal [2] other sites [7].
5	Hudes, et al. 2000 [19]	POH/ oral	Phase 1 (DE, PK, AE)	No	17	Solid tumors (refractory): colon [9], renal [3], lung [2], parotid [2], unknown primary site [1].
6	Murren, et al. 2002 [20]	POH/ oral	Phase 1 (DE, PK)	No	21	Cancer (refractory): pancreas [2], GI [6], ovary [2], NSCLC [2], breast [3], other sites [6].
7	Bailey, et al. 2002 [27]	POH/ oral	Phase 2 (UC, DE, SR)	No	20	Ovary cancer (advanced).
8	Meadows, et al. 2002 [28]	POH/ oral	Phase 2 (UC, DE, SR)	No	27	Colorectal cancer (metastatic).
9	Meadows, et al. 2003 [29]	POH/ oral	Phase 1 (DE, PK)	No	19	Solid tumors (refractory): renal cell CA [4], soft-tissue SA [4], melanoma [2], parotid [2], other sites [9].
10	Azzoli, et al. 2003 [22]	POH/ oral	Phase 1 (DE, PK)	No	21	Solid tumors (advanced).
11	Liu, et al. 2003 [29]	POH/ oral	Phase 2 (UC, SR, PK)	No	15	Prostate cancer (metastatic androgen-independent).
12	Bailey, et al. 2004 [31]	POH/ oral	Phase 1 (DE, PK, AE)	No	20	Solid tumors (advanced): colorectal [5], prostate [2], SA [2], breast [2], NSCLC [2], NHL [2] others [5].
13	Stearns, et al. 2004 [32]	POH/ oral	Phase 1 (DE, AE)	No	37	Breast cancer.
14	Matos, et al. 2008 [15]	POH/ oral	Phase 1	No	8	Pancreatic cancer.
15	Bailey, et al. 2008 [7]	POH/ oral	Phase 2 (UC, DE SR, PK)	No	14	Breast cancer (refractory metastatic).
16	Stratton, et al. 2008 [23]	POH/ dermal	Phase 1 (HV, RCT)	Placebo	25	Normal healthy skin (healthy subjects).
18	Fonseca, et al. 2008 [24]	POH/ intranasal	Phase 1/2 (UC, CS, SR)	No	37	Glioblastoma multiforme [29], anaplastic astrocytoma [5], anaplastic oligodendroglioma [3].
17	Stratton, et al. 2010 [26]	POH/ dermal	Phase 2 (RCT, AE)	Placebo	83	Skin actinic damage (preneoplasic lesion).
19	Fonseca, et al. 2011 [30]	POH/ intranasal	Phase 1/2 (DE, CT, SR)	Hist. Control*	89	Glioblastoma multiforme (recurrent).
20	Fonseca, et al. 2013 [25]	POH/ intranasal	Cohort (Ret.) (DE, CS, SR)	No	198	Glioblastoma multiforme [43], anaplastic astrocytoma [27], anaplastic oligodendroglioma [16].
21	Santos, et al. (2018) [35]	POH/ intranasal	Phase 2 (SR)	Difer. diets	32	Glioblastoma multiforme: ketogenic diet [17], standard diet [15].

*89 GBM patients treated with POH were matched with 52 GBM patients of untreated (supportive therapy only) historical control; GI: Gastrointestinal; NSCLC: Non-Small Cell Lung Carcinoma; CA: Carcinoma; SA: Sarcoma; NHL: Non-Hodgkin's Lymphoma; PK: Pharmacokinetic data; RCT: Randomized Controlled Trial; Ret.: Retrospective; CT: Controlled Trial; UC: Uncontrolled Phase 2 Trial; CS: Case Series; DE: Dose Escalation Design; SR: Safety and Apparent Response; AE: Alternative Molecular Endpoints / Surrogate End Point Biomarkers; HV: Healthy Volunteers

patients [16 to 37] with a variety of malignant solid tumors (advanced, metastatic, or refractory) reported data on the safety of POH administered by the oral route (capsules with 250 mg of POH) (Tables 1,2). In eight of these studies, a dose escalation design was used to find the MTD, which ranged from 4.8 to 8.4 g/m^2 per day or 1.6 to 2.8 g/m^2 tid. In one phase I study [15] only one dose level (4.8 g/m^2 per day or 1.2 g/m^2 qid) was tested (Table 1). Adverse effects reported in all trials were gastrointestinal (GI) symptoms such as nausea, vomiting, anorexia, satiety, heartburn, unpleasant taste, eructation, GI reflux, and diarrhea, which appeared to be dose related. Fatigue (most trials), hypokalaemia (02 trials) [19,31], headache (02 trials) [32,15] and CNS depression symptoms such as disorientation, slurred speech, and impaired concentration (one trial) [20] were also reported (Table 2). Seven trials provided data on POH kinetics after oral dosing and reported that metabolites such as PA and DHPA – but not POH – were found in patients' plasma and urine samples [17-22,31]. Overall, kinetic data from these phases I trials suggested that orally administered POH is absorbed and promptly oxidized to PA and DHPA metabolites, which are eliminated through the urine. In summary, results from nine phases; phase I studies indicated consistently that patients with a variety of advanced solid tumors (Table 1) refractory to treatment tolerated high oral doses of POH (Table 2) with GI adverse effects (mostly nausea and vomiting) being the dose-limiting events.

Four single-arm phase II studies provided data on the safety and potential efficacy of oral formulations of POH (250 mg capsules) in the treatment of advanced ovarian cancer [27], metastatic colorectal cancer [28], metastatic androgen-independent prostate cancer [29] and therapy-refractory metastatic breast cancer [7] . Three of these studies were dose-ranging trials with a dose escalation design [7,27,28] and two studies [7,29] also obtained PK data (Tables 1 and 3). Overall, the phase II studies involving the administration of POH by the oral route found no consistent evidence of a potential clinical benefit to cancer patients (Table 3). Results from one study indicated that, in 20 patients with advanced ovary carcinoma, POH (1200 mg/m2/dose TID, 28-day courses) did not prolong overall survival (OS), nor did it enhance progression-free survival (PFS) and progression-free rate. Although the treatment compliance was greater than 90%, GI symptoms limited the escalation of the starting dose to 1500 mg/m^2/dose

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Table 2: Phase I clinical trials on the safety of administration of limonene or perillyl alcohol to cancer patients.

Study (ref.)	Patients		Doses	MTD	Adverse Events (AE)
	N	Cancer			
				D-Limonene – Oral	
Vigushin, et al. 1998 [16]	32	Solid tumors	0.5-1.2g/m2/d 21-d cycles	8 g/m2/d	Dose-related nausea, vomiting and diarrhea. Most AE were Grade I or II. No Grade IV (serious organ toxicity) was noted.
				Perillyl Alcohol- Oral	
Ripple, et al. 1998 [17]	18	Solid tumors	0.8 to 2.4 g/m2/dose tid	2.4 g/m2 (1.6 g/m2)+	Dose-related GI toxicity, nausea, vomiting, diarrhea, anorexia, satiety, eructation, unpleasant taste, fatigue. Almost all were Grade I or II AE. Only one Grade IV (reduced absolute neutrophil count) was recorded.
Ripple, et al. 2000 [18]	16	Solid tumors	0.8 to 1.6 g/m2/dose tid	> 1.6 g/m2	Dose-related GI toxicity, nausea, vomiting, diarrhea, anorexia, satiety, eructation, unpleasant taste, fatigue (mostly Grade I). Trombocytopenia (grade I) one patient.
Hudes, et al. 2000 [19]	17	Solid tumors	1.6 to 2.8 g/m2/dose tid	2.8 g/m2	Hypokalaemia, discom, vomiting, pyrosis, fatigue, diarrhea, anorexia, stomatitis, nausea, vomiting, pyrosis, fatigue, diarrhea, anorexia. Most AE were Grade I.
Murren, et al. 2002 [20]	21	Solid tumors	1.6 to 2.8 g/m2/ dose	2.1 g/m2	GI toxicity; nausea, vomiting, diarrhea, fatigue, CNS toxicity: disorientation, impaired concentration, tinnitus, slurred speech.
Meadows, et al. 2003 [21]	19	Solid tumors	1.35 to 4.05 g/dose qid 28-d cycles	> 4.05 g/dose qid	GI toxicity: nausea, vomiting, heartburn, indigestion, most cases were Grade I AE.
Azzoli, et al. 2003 [22]	21	Solid tumors	4.8 to 11.2 g/m2/d	8.4 g/m2/d	Dose-related GI toxicity: nausea and vomiting (all patients).
Bailey, et al. 2004 [31]	20	Solid tumors	1.2 to 2.0 g/m2/dose	> 2.0 g/m2	Dose-related GI toxicity: Nausea, vomiting, fatigue, GI distress (bloatig, discomfortation or pain, eructation), diarrhea, early satiety, constipation and hypokaelemia. Most cases were Grade I or II AE. No Grade IV AE was noted. One case of acute pancreatitis.
Stearns, et al. 2004 [32]	37	Breast	1.2 to 4.8 g/m2/dx 2d	> 4.8 g/m2	GI reflux, fatigue, headache, elevated bilirubin, elevated White cell count, hot flash, erythema, hypertension. All cases were Grade I AE.
Matos, et al. 2008 [15]	8	Pancreas	1.2g/m2/dose qid x 15d	> 1.2 g/m2/dose qid	GI toxicity: diarrhea, vomiting, nausea, constipation, ankle discomfort, headache, most cases were Grade I or II AE.
				Perillyl Alcohol- Dermal	
Stratton, et al. 2008 [23]	25	Normal healthy skin.	Cream 0.76% w/w, twice daily for 30 d	> 0.76% twice daily	No serious cutaneous, systemic or histopathological abnormalities were noted.8 subjects reported mild daily AE including reversible appearance of 1 to 2 small papules.
				Perillyl Alcohol- Intranasal	
Fonseca, et al. 2008 [35]	37	GBM, AA, AO	0.3% v/v (55 mg) qid (total: 220 mg/d)	> 55 mg qid	No patient presented signs of toxicity.
Fonseca, et al. 2013 [25]	198	GBM, AA, AO	0.3% v/v (55 mg), 533.6 mg/d	> 533.6 mg/d	Occasional nose soreness, nose bleeding (rare).

MTD: Maximum Tolerated Dose; GI: Gastrointestinal; d: day; AE: Adverse Events; ND: Not Determined; Grading: Common Terminology Criteria (CTC) for Adverse Events – National Cancer Institute. +Only one patient (nausea) treated with 1.6 g/m2 met criteria for DLT: (Dose Limiting Toxicity). GBM: Glioblastoma Multiforme; AA: Anaplastic Astrocytoma; AO: Anaplastic Oligodendroglioma.

[27]. In 27 patients with metastatic colorectal cancer, POH (1200 mg/m²/dose QID with a possible escalation to 1600 mg/m²/dose after 4 weeks) did not increase the time to disease progression (TTP) (treated group median: 1.8 months, range: 1-3 months. In this case, the historical control median of TTP was assumed to be 4 months) and no colorectal carcinoma patient exhibited a complete or partial response to treatment [28].

A study with metastatic androgen-independent prostate cancer patients (N = 15) treated with POH (1200 mg/m²/dose po QID, 1.8 cycles of 4 weeks) led to no evidence of clinical benefit; either the patients' disease progressed, or they withdrew from the trial due to drug intolerance (nausea/vomiting) within 6 months of receiving POH (the primary efficacy endpoint of the trial was 6-month PFS) [29]. One study of POH (1200-1500 mg/m²/dose QID, 29 cycles of 28 days) conducted on women with treatment-refractory metastatic breast cancer (n = 14), did not find any evidence of clinical benefit either. No objective clinical responses were noted; for one year the FFP rate (primary efficacy endpoint) was zero, and the median (95% CI) TTP and OS were 35 (29-123) days and 389 (202-776) days, respectively [7].

Data on the kinetics of POH after oral administration were obtained from two phase II studies (Table 3). As noted in phase I trials, POH metabolites (PA and DHPA) but not the unmetabolized drug were detected in the patient's plasma after treatment by the oral route. One study [7] found, in a subset of three breast cancer women receiving 1200 mg of POH/m² (on day 1 of cycle 1), the following kinetic data for PA and DHPA (mean ± SD): PA, C_{max} = 371 ± 191 µM, AUC_{0-6h} = 929 ± 643 µM.h, $t_{1/2}$ = 1.2 ± 0.8 h; DHPA, C_{max} = 27 ± 20 µM, AUC_{0-6h} = 96 ± 78 µM.h, $t_{1/2}$ = 5 ± 3h (Table 3). Another study [29] found plasma levels of PA and DHPA as high as 224 ± 171 µM and (22 ± 14 µM, respectively, in prostate cancer patients 2 h after the last POH (1200 mg/m²) ingestion. These kinetic findings were consistent with those obtained in previous phase I trials and indicated that, after oral administration, POH is promptly absorbed and converted to its major acid metabolites (mainly PA) which are also rapidly (half-live 5 h) cleared from the plasma.

Like prior phase I trials, adverse events noted in phase II studies of oral POH were mostly complaints of fatigue, and GI-related symptoms such as nausea/vomiting, bloating and eructation, satiety and anorexia, and diarrhea (Table 3). One

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Table 3: Clinical trials (phase II) on the safety and efficacy of limonene and perillyl alcohol in the treatment of cancer.

Patients (N)	Cancer	Comparator Statistics	Dosing schedule	Kinetics	Outcomes			Ref.
					Safety	Efficacy		
						Endpoints	Results	
d-Limonene – Oral								
10	Breast	No	8000 mg/m²/d 15 cycles of 21 d.	Plasma: limonene (10.8 to 20.5 μM); PA (20.7 μM), DHPA (16.6 μM); limonene-diol; uroterpenol	GI symptoms: Nausea, vomiting and diarrhea (dose-limiting).	No data	No response in 7 patients who completed one or more cycles of treatment (8 g/m²/d).	[16]
Perillyl alcohol - Oral								
20	Ovary (Adv.)	No	1200 mg/m²/dose TID; cycles of 28 d. with possible escalation to 1500 mg/m²/dose after 28d.	No data	GI symptoms: Nausea, satiety, eructation. Fatigue.	OS, TTP, PFS. Significant clinical benefit: 6 months freedom of progression.	Median OS 9.1 mo, median PFS 1.7 mo, 6 mo PF rate 17%, no patient exhibited a complete or partial response.	[27]
27	Colorectal (Met.)	No	1200 mg/m²/dose QID; with possible escalation to1600 mg/m²/dose after 4 weeks.	No data	GI symptoms: belching, bloating, nausea, vomiting, anorexia. Fatigue.	TTP. Historical control median TTP = 4 months.	Median TTP 1.8 mo (range 1 to 3 mo). No patient exhibited a complete or partial response.	[28]
15	Prostate (Met.Ar)	No	1200 mg/m²/dose QID.	Plasma: PA (224±171 μM); DHPA (22±14 μM)	GI symptoms: nNausea, vomiting. Fatigue. Hypokalemia.	6-mo progression free survival (PFS) benefit.	All patients either progressed or withdrew from the trial due to drug intolerance before 6 mo.	[29]
14	Breast (Met Ref)	No	1200-1500 mg/m²/dose QID; 29 cycles of 28 d.	Plasma: PA (C_{max} 371 ± 191 μM) and DHPA (C_{max} 27 ± 20 μM)	GI symptoms: Nausea, vomiting, bloating, diarrhea. Fatigue.	Primary endpoint: One-year freedom from progression rate (FFP).	One-year FFP rate 0; Median TTP 35 d (95% CI, 29-123 d); Median OS 389 d (95% CI, 202-776 d).	[7]
Perillyl alcohol - Dermal								
86 +	§ Actinic keratoses	# Placebo Non-parametric tests	Cream 0.3 and 0.76% w/w, twice daily for 3 months Treated vs Control; forearm.	No data	No topical or systemic significant adverse effect.	Reversal of actinic damage as evidenced by normalization of quantitative skin histopathologic scores and change in nuclear chromatin pattern.	Except for a reduction in nuclear chromatin abnormality (by 16.4%, $p < 0.01$) at the highest dose (0.76% POH), there was no response to treatment.	[26]
Perillyl alcohol - Intranasal								
89	GBM (Rec)	Hist. Cont. Kaplan-Mayer curves and log rank test	* Intranasal delivery 4 x daily, 0.3% v/v (55 mg) qid (220 mg/d) with escalation up to 440 mg/d.	No data	No apparent side effect.	Overall survival (OS).	Treated primary GBM patients mean OS longer (5.9 mo) than historical control group patients (2.3 mo) ($p < 0.0001$). Median OS of treated patients with secondary GBM even longer (11.2 mo).	[30]

Adv.: Advanced; Met.: Metastatic; Ar: Androgen resistant; Met Ref: Metastatic Refractory to Treatment; Rec.: Recurrent.GI: Gastrointestinal; PA: Perillic Acid; DHPA: Dihydroperillic Acid; TID: Three Times Daily; QID: Four Times Daily; mo: months; OS: Overall Survival; TTP: Time to Progression; PFS: Progression Free Survival; FFP: Freedom from Progression Rate; GBM: Glioblastoma Multiforme. +After randomization (RCT); KD: Ketogenic Diet; PR: Partial Response (≥ 30% decrease in targeted lesion); PD: Progressive Disease. #Kruskal-Wallis test, Wilcoxon rank sum test. *Limiting dose to avoid nasal discomfort. §Actinic keratoses are intra-epithelial skinneoplasms thatmay evolve to squamous cell carcinoma.

study also reported a probable (grade 4) treatment-related hypokalaemia [29]. Treatment-related GI intolerance and fatigue were reported to be major obstacles for dose escalation [5,27], and or the reasons for POH discontinuation [29] and patient withdrawal from the study [28]. In summary, four phase II trials of oral POH in patients with ovary, colorectal prostate, and breast advanced cancers, metastatic and refractory to treatment, suggested that repeated administration of this monoterpenoid drug up the MTD produced no discernible clinical benefit.

Trials involving dermal application of perillyl alcohol

Based on previous studies showing that topically applied POH inhibited UV-B induced skin carcinogenesis in mouse skin [33,34], this monoterpenoid alcohol was tested in two clinical trials. In a first human test (phase I) [23], the effects (safety and histopathological changes) of a POH cream (0.76% wt/wt) on the skin were investigated in randomized 25 healthy subjects. This was a controlled (double-blinded) study and the subjects had POH cream applied to one forearm and the placebo cream to the other daily for 30 days. The POH cream produced no serious topical (skin) or systemic toxicities, with no significant difference between lesions appearing on the POH-treated forearm *versus* those on the placebo-treated forearm. A phase II (double-blinded, randomized, placebo-controlled) trial evaluated the efficacy of POH creams (0.3 and 0.76% w/w, applied twice daily for 3 months) in reversing sun-damaged skin (actinic keratosis) on the dorsal forearm of 89 patients

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Table 4: Assessment of the methodological quality of phase II clinical trials providing data on the safety and efficacy of limonene and perillyl alcohol in the treatment of cancer.

Study (ref.)	Drug / Population	Study design	Assessment of methodological quality of case series according to Murad, et al. [24]§				
			Domains				
			Selection	Ascertainment	Causality		Reporting
Vigushin, et al. 1998 [16]	LIM / 10 breast cancer patients	Single arm	1-Unclear	2- Exposure: Yes 3- Outcome: Yes	4- Alternative causes ruled out: No 6- Dose-response: No	5- Challenge/rechallenge: No 7 – Follow-up suficient: No	8- Sufficient details: No
Bailey, et al. 2002 [27]	POH / 20 advanced ovary cancer patients	Single arm	1-Yes	2- Exposure: Yes 3- Outcome: Yes	4- Alternative causes ruled out: No 6- Dose-response: No	5- Challenge/rechallenge: No 7 – Follow-up suficient: Yes	8- Sufficient details: Yes
Meadows, et al. 2002 [28]	POH / 27 metastatic colorectal cancer patients	Single arm	1-Yes	2- Exposure: Yes 3- Outcome: Yes	4- Alternative causes ruled out: No 6- Dose-response: No	5- Challenge/rechallenge: No 7 – Follow-up suficient: Yes	8- Sufficient details: Yes
Liu, et al. 2003. [29]	POH / 15 prostate cancer patients	Single arm	1 -Yes	2- Exposure: Yes 3- Outcome: Yes	4- Alternative causes ruled out: No 6- Dose-response: No	5- Challenge/rechallenge: No 7 – Follow-up suficient: Yes	8- Sufficient details: No
Bailey, et al. 2008 [7]	POH / 14 metastatic breast cancer patients	Single arm	1-Yes	2- Exposure: Yes 3- Outcome: Yes	4- Alternative causes ruled out: No 6- Dose-response: No	5- Challenge/rechallenge: No 7 – Follow-up suficient: Yes	8- Sufficient details: No
Fonseca, et al. 2011 [30]	POH / 89 patients with recurrent glioblastoma	Comparator: Hist. Control ⁺	1-Yes	2- Exposure: Yes 3- Outcome: Yes	4- Alternative causes ruled out: No 6- Dose-response: No	5- Challenge/rechallenge: No 7 – Follow-up suficient: Yes	8- Sufficient details: Yes
Santos, et al. 2018 [35]	POH / 32 patients with recurrent glioblastoma	Two arms: POH: POH+KD x POH+StD	1-Yes	2- Exposure: Yes 3- Outcome: Yes	4- Alternative causes ruled out: No 6- Dose-response: No	5- Challenge/rechallenge: No 7 – Follow-up suficient: Yes	8- Sufficient details: Yes

Study (ref.)	Drug / Population	Study design	Assessment of risk of bias (High, Low or Unclear) of randomized controlled clinical trial (RCT)			
			Selection bias		Performance bias	Detection bias	Attrition bias
Stratton, et al. 2010 [26]	POH / 83 patients with > 2 actinic keratoses randomized, placebocontrolled	RCT Double-blind, randomized, placebo control	Random sequence High	Allocation concealment High	Blinding of participants & subjects Unclear	Blinding of outcome assessment Low	Incomplete outcome data Low

LIM: d-limonene. POH: Perillyl Alcohol. RCT: Randomized Controlled Trial. GI: Gastrointestinal; PA: Perillic Acid; DHPA: Dihydroperillic Acid; TID: Three Times Daily; QID: Four Times Daily; OS: Overall Survival; TTP: Time To Progression; PFS: Progression Free Survival; FPR: Freedom From Progression Rate; GBM: Glioblastoma Multiforme. ⁺Comparator: 52 GBM patients of untreated (supportive therapy only) historical control. KD: ketogenic diet; StD: standard diet. §Murad, et al. 's tool, comprises binary responses (yes, no) to 8 questions categorized into 4 domains (Selection, Ascertainment, Causality and Reporting): 1 - Does the patient (s) represent (s) the whole experience of the investigator (centre) or is the selection method unclear to the extent that other patients with similar presentation may not have been reported? 2 - Was the exposure adequately ascertained? 3 - Was the outcome adequately ascertained? 4 - Were other alternative causes that may explain the observation ruled out? 5 - Was there a challenge/rechallenge phenomenon? 6 - Was there a dose-response effect? 7 Was follow-up long enough for outcomes to occur? 8 - Is the case (s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners make inferences related to their own practice?"

(0.3% = 27, 0.76% = 28, placebo = 28 patients) [26] (Table 3). Baseline and end-of-study biopsies were taken to evaluate POH cream effectiveness in reversing actinic damage, as evidenced by normalization of skin histopathologic scores and karyometric analysis of nuclear chromatin pattern. The results suggested that, whereas no changes were observed in p53 expression, cellular proliferation (by proliferating cell nuclear antigen expression), or apoptosis in either treatment group compared with the placebo group, the 0.76% POH cream had a modest effect in reducing nuclear abnormality in moderately to severely sun-damaged skin [26]. In summary, data from one randomized and controlled trial of a cream formulation of POH largely failed to provide evidence that it could be effective in reversing actinic keratosis, a precancerous lesion.

Trials involving intranasal instillation of perillyl alcohol

Since 2008, four reports have been published on the interim results of an ongoing phase I/2 clinical study of intranasal POH in the treatment of recurrent gliomas [24,25,30]. In the former assay [24], POH was given by intranasal instillation (0.3% v/v solution, 55 mg, 4 times daily, or 220 mg/day) to 37 patients with recurrent malignant gliomas (i.e., 29 with glioblastoma multiforme, five with anaplastic astrocytoma, three with anaplastic oligodendroglioma) and patients' clinical response was evaluated by neurological examination and magnetic resonance imaging (MRI). In this case, a complete response (CR) was the disappearance of all enhancing tumors on consecutive MRIs, with corticosteroid discontinuation and neurologic stability or improvement, while a partial response (PR) was 50% or greater reduction in the size of the tumor with stability or improvement. A 25% or greater increase in tumor size or a new lesion was defined as a "progressive disease". With a medium follow-up of 48 weeks, no POH toxicity was apparent and the 6-month PFS (partial response and stable disease) rates were 48.2%, 60%, and 66.6% for patients with GBM, anaplastic astrocytoma, and anaplastic oligodendroma, respectively. A further report [30] (phase I/2 trial) provided data on the response of 89 patients with recurrent glioblastoma to POH (intranasal instillation 4x daily, 440 mg/day) compared to an untreated historical control group (years 2005-2009) of 52 patients with GBM. The OS of patients with primary GBM treated with POH was significantly longer (Kaplan-Meyer plot, $p < 0.0001$) than that of GBM patients in the untreated historical control group. The third article [25] presented data (phase II) on the response of 198 patients [117 men and 81 women; GBM = 155; astrocytoma = 27, oligodendroma = 16] to long-term therapy with intranasal POH (4 times daily, starting from 66.7 mg/dose or 266 mg/day with escalation to 133.4 mg/dose or 533.6 mg/day). According to the investigators, POH occasionally caused nose soreness and bleeding at the highest dose level (533.6 mg/day) and, after 4 years, 19% of patients treated with the monoterpene alcohol as monotherapy remained in clinical

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remission (Tables 1,2). Moreover, a two-arm controlled trial by Santos, et al. [35] investigated whether a ketogenic diet (KD) administered for 3 months would improve the clinical response of recurrent glioblastoma patients to treatment with POH. The patients well-tolerated treatment with POH and clinical responses (KD, N=17 vs Standard diet, N=15) were as follows: partial response 77.8% vs 25%; stable disease 11.1% vs 25%, progressive disease 11.1% vs 50%.

Three additional studies investigated factors that might have influenced the response of the patients enrolled in the POH trial. These studies addressed a possible influence of glutathione S-transferase mu 1 and glutathione S-transferase theta 1 [36] and epidermal growth factor *61A/G* (EGF+61A>G) [37] polymorphisms on the survival rate and possible molecular interaction of the monoterpene alcohol with glioma cell plasma membrane [38]. Overall, data on the clinical response of this group of patients with central nervous tumors (mostly recurrent glioblastoma (GBM), one of the most malignant types) to intranasal POH suggested that it is generally well-tolerated, has antitumor activity, and prolongs overall survival. GBM has a poor prognosis, tumors tend to recur after current standard treatments, and patients generally die within 14 months of diagnosis. Within this context, the results from these phase I/2 trials suggested that intranasal POH might eventually become an innovative therapeutic approach in neuro-oncology. Owing to the limitations of these open, uncontrolled, and nonrandomized trials, however, any conclusion on the clinical efficacy of POH would be premature.

Discussion

The clinical evidence on the putative anticancer activity of perillic monoterpenoids is limited to phase I and II trials in which *d*-limonene (oral) or POH (oral, topical, intranasal) were administered to patients with several types of malignancies. These studies were generally nonrandomized and uncontrolled trials (using at best historical controls) and thus all of them had a high risk of bias. All the four phase II trials of orally administered POH [7,27-29] and the one with *d*-limonene [16], failed to reveal indications of efficacy, a clinical research outcome that discouraged conducting further phase III studies of these compounds. As mentioned above, nausea, vomiting, diarrhea, and other GI symptoms caused by oral POH (and *d*-limonene) were dose-limiting adverse effects, and 1200 mg/m^2/dose (TID or QID) was generally the highest (MTD) dose tested in phase II studies of POH. Based on results from the phase I studies, one could speculate that some evidence of efficacy might emerge at higher oral doses (1600 mg/m^2/dose, or higher, TID or QID) or if a better oral formulation of POH was developed. Notably, it is necessary to take a large number of capsules daily (up to 90 per day) to achieve the target doses of POH in phase I/II trials [19]. In most trials, the tested drug (500 mg capsules) contained 250 mg of POH plus 250 mg of soybean oil. Since some GI symptoms could arise from ingesting such a large volume of soybean oil, a new oral formulation of POH consisting of 700 mg capsules containing 675 mg of the active ingredient (POH) was tested [21]. This new formulation was well-tolerated, although no improvement in efficacy was apparent.

In contrast to trials of orally delivered POH, a phase II study of intranasal POH suggested that it might be an effective treatment for recurrent malignant gliomas. Apart from possible disadvantages of intranasal drug delivery (*e.g.*, the extent of absorption depends on nasal mucosa health and blood flow) no therapy-related toxicity emerged, and this route of administration was effective and safe for delivering POH to the brain. Although the fact that the study was open (not blinded), and primary efficacy endpoints in treated patients were compared to those in the historical control group (no within-trial controls, no randomization) a significantly longer OS in the treated group seemed to indicate that intranasal POH was effective. It is of note that doses of POH given in trials with intranasal dosing were much lower than the doses administered in trials with oral dosing. In the studies with intranasal dosing, all GBM patients (regardless of their body weights and body surface areas-BSA) received a fixed dose of 440 mg of POH per day. Since patients' body weight or BSA were not reported by the authors of the study, it was not possible to express the doses given by intranasal administration as mg/m^2. For comparison purposes, if a patient 170 cm tall weighing 70 kg had received 440 mg of POH a day, the dose would have been 242 mg of POH/m^2 per day according to Mosteller's formula to calculate BSA [BSA (m^2) = (height (cm) x weight (kg)/ 3600)$^{1/2}$], this hypothetical patient would have a BSA of 1.818 m^2 [39].

Analytical data from phase I/II trials demonstrated that PA (major metabolite) and, to a lesser extent DHPA, were consistently detected in patients' plasma (or urine) one to two hours after an oral dose of POH [7,17,20,22,29,31]. These findings (including occasional traces of POH) are consistent with data from other studies of limonene and metabolite kinetics in humans [40]. Kinetic data, therefore, suggest that liver (phase-I) drug metabolism enzymes promptly and extensively convert POH into PA. One of the advantages of intranasal drug delivery is that, as in sublingual administration, it circumvents liver first pass metabolism and, by doing so, intranasal instillation is likely to improve the bioavailability of POH compared to that following oral administration. Moreover, there is evidence that some molecules can be transported across the olfactory mucosa directly into the cerebral spinal fluid (CSF), giving rise to CSF concentrations higher than those reached in the blood plasma [41]. Therefore, differences between POH kinetics after intranasal and oral administration could explain why it presented apparent anticancer activity when it was delivered via the nasal cavity mucosa, but not when it was given orally. Unfortunately, the clinical study involving intranasal POH delivery did not provide any complementary data on patients' plasma and/or CSF levels of POH, and its major metabolites (PA, DHPA, or others) to corroborate this interpretation. The molecular mechanism involved in glioma therapy by intranasal POH and nose-to-brain transport has been investigated recently [42,43]. In this direction, a similar clinical phase I/IIa study of intranasally delivered highly purified POH (> 99%) in GBM patients is currently ongoing in the U.S. (ID: NCT02704858). The US study design should provide complementary PK data on intranasal administered POH during Phase I at first dosing, and after the first dose of the 3rd cycle of treatment. The results from phase

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I/II studies suggesting that intranasal POH was effective in treating recurrent malignant gliomas are encouraging but need to be confirmed by controlled, blind and randomized (phase III) trials and robust statistical analysis. Finally, although no development of oncologic drugs based on perillic derivatives has been completed thus far, these small molecules still have potential therapeutic usefulness to be further explored, particularly as drugs to treat glioblastoma.

Acknowledgment

The authors thank Gabrielle P. das Neves, for the help with updating the original review.

Funding

This work was supported by the CNPq-PROEP/FAR/Fiocruz under grants 407841/2017-2 and 440023/2022-0.

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