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Review

Boswellia: A Systematic Review of the Adverse Events

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Abstract

Boswellia is one of the oldest alternative medicinal plants in the world. Boswellia is thought to have anti-inflammatory effects, antioxidant properties, and immunity stimulating. This herbal medicine relieves several diseases such as osteoarthritis, asthma, and inflammatory bowel diseases. Little is known about the adverse drug reactions of Boswellia; this systematic review attempted to identify the potential side effects of this supplement and its severity in different diseases. Relevant studies conducted up to May 2024 were identified from Scopus, Science Direct, Web of Science, PubMed, Cochrane Library, and Embase databases. Spontaneous reports about the side effects of Boswellia were gathered from three international spontaneous reporting schemes, as well. Age, sex, type of disease, dosage, and duration of the drug as well as self-reported side effects were considered. Subgroup analysis was performed to determine the prevalence of each adverse effect of Boswellia. The quality of the included trials was assessed using version 2 of the Cochrane risk-of-bias tool (RoB 2). Sixty-two clinical trials were included in this review. Twenty-five of them reported side effects. Twenty-seven studies reported that Boswellia had no adverse effects, and 10 articles had not mentioned the side effects. Low-to-high risk of bias was found in clinical trials. Ten case reports were included in this study, but no case series was included. Spontaneous reporting schemes included 26 reports. The most common adverse effects were gastrointestinal disorders and cutaneous allergic reactions. Although most detected adverse effects were mild to moderate, two patients developed hypersensitivity pneumonitis and bezoar formation, respectively. This systematic study reported that Boswellia, as an herbal medicine, is often considered safe to use; however, it is possible to experience severe side effects. We suggest that Boswellia should be administered only under the supervision of a specialist doctor in usual medical treatment.

Keywords: Adverse effect; Boswellia; Clinical trial; Frankincense; Systematic review

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Introduction

Boswellia resin has a long history of use as an herbal remedy [1], and there is worldwide demand for using it in folk medicine and religious ceremonies. It is an aromatic resin taken from trees of*Boswellia* species [2,3]. The resin of this plant is popularly known as "Frankincense", "olibanum", "salai guggal", "loban", or "kundur" (Figure 1) [1,4]. It is obtained through incision on the trunks of Boswellia trees [4]. The Boswellia tree has 25 species from the genus *Boswellia* and Burseraceae family. It is native to Arabia and India, but it has been used as a remedy for thousands of years in many regions such as China and Africa [1]. At present, the popularity of Boswellia is increasing in Western and European countries, and different animal studies and clinical trials confirm the therapeutic potential of this herbal remedy [4,5].

The composition of Boswellia varies in different species and depends on the climate, time of harvest, and geographical location. Oleo gum resin of Boswellia contains 30–60% resin (including higher terpenoids), 5–12% essential oil (mainly contains monoterpenoids which includes α-pinene) as well as polysaccharides (~65% arabinose, galactose, and xylose) and polymeric substances in limited extent [6-8]. The presence of pentacyclic triterpenes or boswellic acids (BAs) as bioactive compounds in almost all species is the main characteristic feature of the genus *Boswellia* (Figure 2) [2,7]. BAs such as acetyl-11-keto-β-boswellic acid (AKBA), 11-keto-b-bos-wellic acid (KBA), and β-boswellic acid (BBA) are responsible for most of the therapeutic effects of Boswellia. Boswellic acid interfered with COX-1 and inhibits the activity of 5-lipooxygenase; as a result, leukotrienes decrease. Another mechanism of boswellic acid is inhibition of the activity of serine protease cathepsin G and microsomal prostaglandin E synthase-1 [6,7]. Thus, Boswellia has an anti-inflammatory effect on several disorders such as osteoarthritis, rheumatism, inflammatory bowel disease, and asthma [1]. It has antidiabetic effect in type 1 and 2 diabetes mellitus. In addition, lipophilicity of BAs allows them to pass through the blood-brain barrier. Also, Boswellia increases memory and learning, so it has been used in the treatment of central nervous system (CNS) diseases and the prenatal period for memory enhancement of the newborn [7,9,10]. According to scientific studies, Boswellia has other advantages such as antitumor, immunomodulatory, antiseptic, analgesic, anxiolytic, and antioxidant activities [11]. AKBA and KBA reach peak concentrations up to 4 hours when administered alone [12]. The extract of Boswellia is a potent, non-selective inhibitor of CYP450 metabolizing enzymes CYP1A2/2C8/2C9/2C19/2D6 and 3A4, with considerable potential for drug-herb interactions [6].

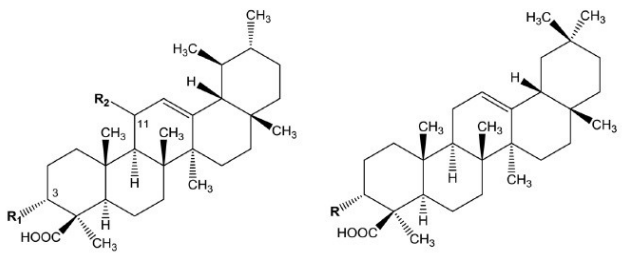
There are many studies that have evaluated different characteristics of the genus *Boswellia* and described the benefits of this popular plant. In medicine, it is important to know the toxicity and adverse effects of herbal remedies because herbs are not completely safe [13]. Adverse drug reaction is unintentional and noxious reaction that occurs at the usual dose of the drug for prophylaxis, diagnosis, or treatment of diseases [14]. Complementary and alternative medicine is extensively used in the world and herbal medicine has a veritable effect in the treatment of many diseases [15,16]. However, there is no systematic review study about the side effects of different *Boswellia* species; therefore, we decided to evaluate the side effects and safety of this genus in human studies and spontaneous reporting schemes as a systematic review.

Methods

Search strategy

A systematic literature search was electronically conducted up to May 2024 in the following databases: Scopus, Science Direct, Web of Science, PubMed,

Figure 1. Picture of Boswellia



	R_1	R_2
1	α-CH_3COO	O
3	α-CH_3COO	H/H
4	α-OH	O
6	α-OH	H/H

	R
2	α-CH_3COO
5	α-OH

Figure 2. Chemical structures of the boswellic acids available as standards; 3-acetyl-11-keto-β-boswellic acid (**1**), 3-acetyl-α-boswellic acid (**2**), 3-acetyl-β-boswellic acid (**3**), 11-keto-β-boswellic acid (**4**), α-boswellic acid (**5**), β-boswellic acid (**6**) [2].

Cochrane Library, and Embase. The selected search terms in PubMed database was (Boswellia[MeSH Major Topic]) OR (Boswellia serrata[Title/Abstract])) OR (Boswellia carteri[Title/Abstract])) OR (Boswellia carterii[Title/Abstract])) OR (Boswellia sacra[Title/Abstract])) OR (Frankincense[MeSH Major Topic])) OR (Olibanum Resin[Title/Abstract])) OR (Resin, Olibanum[Title/Abstract])) OR (Frankincense Resin[Title/Abstract])) OR (Resin, Frankincense[Title/Abstract])) OR (Olibanum[Title/Abstract])) OR (salai guggal[Supplementary Concept])) OR (Sallaki[Title/Abstract])) OR (boswellic acid[Supplementary Concept]. The search field was "Title/Abstract/Keywords" in Scopus and Cochrane Library database, "Title/Abstract" in Embase, "Topic" in Web of Science, and all research articles and case reports in Science Direct. The Boolean operation (i.e. OR) was used between these keywords to combine them. The keywords were searched separately in all databases and imported to Endnote. We reviewed the articles mentioned in the references to make sure we included the articles related to our title.

Study selection

All retrieved data were assessed by two independent reviewers separately. Disagreements were resolved by team discussion. In duplicated reports, we enrolled the searches with more details. As recommended by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [17], the titles and abstracts were checked, and according to inclusion and exclusion criteria irrelevant studies were deleted. Then, the full-text of the articles included in our study was evaluated for eligibility (Figure 3).

Inclusion and exclusion criteria

Our search was limited to human studies, assessing mono-herbal preparation of Boswellia and articles published in the English language. This review included all randomized, non-randomized, and open-label clinical trials, case reports, and case series studies about the side effects of Boswellia. We included data in spontaneous reports about Boswellia adverse effects published in Australian Database of Adverse Event Notifications (DAEN), Canada Vigilance Adverse Reaction Online Database, and World Health Organization (WHO) collaborating center for International Drug Monitoring Database. (Table 4)

We excluded multi-herb products, animal, in-vitro, and molecular studies. Letters to the editor, book selections, and literature without available abstract and full text were excluded as well. There was no language limitation.

Data collection

The data collected from the clinical trials included the number of total and Boswellia group participants who finally participated in the study, their age, health status, drug regimen (preparation form, dose, interval, and duration), species of Boswellia, and side effects. In trials, the mean age was described separately in the groups, and age in the Boswellia group was mentioned in tables. Data collected from case reports included age and gender, health status, drug information (preparation form, dose, interval, and duration), side effects, and outcomes. Data from clinical trials are shown in Tables 1-3 and were designed according to the side effects mentioned in the articles. Case reports were explained in a separate table as well.

Risk of bias assessment

Two researchers independently assessed the risk of bias (RoB) of included trials by using the second version of the Cochrane RoB tool [18]. It consists of five domains to evaluate selection bias (domain 1), performance bias (domain 2), detection bias (domain 3), attrition bias (domain 4), and reporting bias (domain 5) [19].

Each domain was rated as low risk, high risk, or some concerns. Finally, overall risk was rated for the trial [18]. The RoB2 assessment was implemented using an Excel template. Discrepancy was solved by group discussion.

Data analysis

Data extracted from the articles were transferred into Excel tables. We did not have a meta-analysis in this study.

Results

As shown in figure 3, 72 studies were included which contained 62 trials and 10 case reports of Boswellia side effects.

A meta-analysis was not conducted for this study due to inconsistencies in the side effects reported across various studies, as well as the absence of a defined threshold for the incidence of these side effects. Future research should categorize complications more precisely.

Clinical trials

Sixty-two clinical trials were included in this systematic review. Among them, 25 studies reported side effects [20-44], 27 reported that Boswellia had no side effects [45-70], and 10 trials did not mention any data about adverse effects [71-80].

Clinical trials reporting side effects

Twenty-five clinical trials reported the side effects of Boswellia [20-44]. One study was cross-over [27] (Table 1).

The minimum included age was 15 years old [31] and

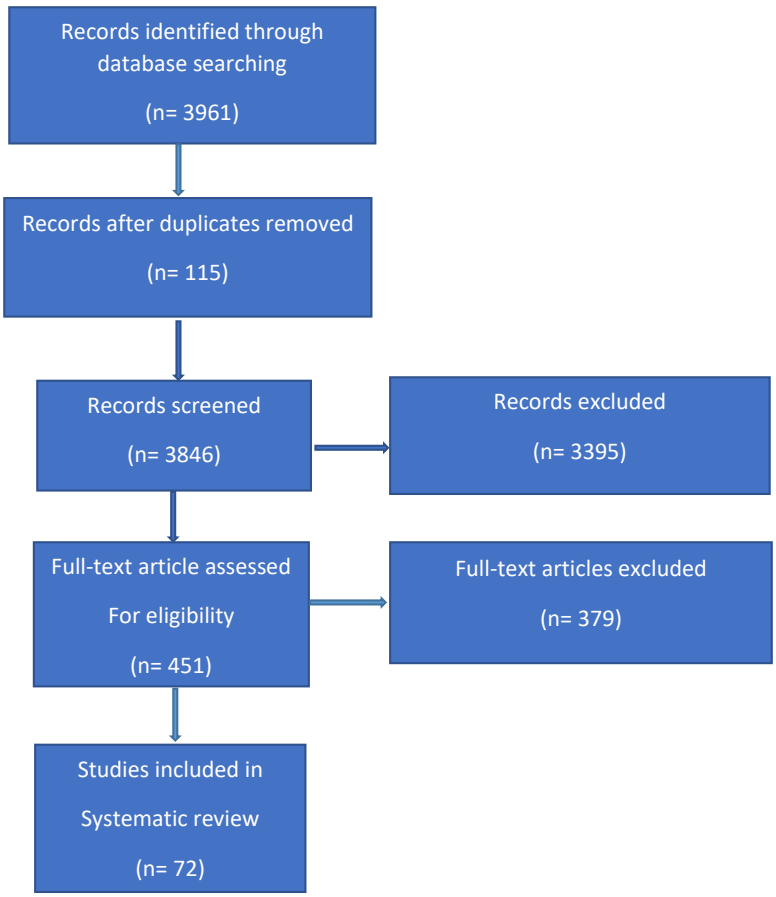


Figure 3. PRISMA flow diagram of the study

the maximum age was 85 years old [37].

The efficacy of Boswellia consumption was evaluated for different disorders. Seven studies were done on knee osteoarthritis [27,34,35,39-41,43], five trials were about intestinal diseases [21,23-25,29], five trials were about neurologic problems [26,28,30,31,37], three trials were on patients with breast problems [32, 33, 42], two of them studied asthma [22,44], and one study investigated rheumatoid arthritis [38], cancer-related fatigue [36] and wound [20].

The herb species, *Boswellia serrata* Roxb. ex Colebr (*B. serrata*) were used in 20 studies [21-31, 34,37-44], *Boswellia sacra* Flueck (Synonym: *Boswellia carteri* Birdw.) (*B. sacra (B. carteri))* was used in three studies [20, 35, 36], and two studies did not mention the species used [32,33].

In all included studies, total of 883 patients were categorized in the Boswellia groups. The treatment duration was between 7 days [28] to 52 weeks [25]. The oral dose was from 100 mg [32,33,39,40, 43] to 3600 mg per day [23]. Except for four studies that used topical form (cream and oil) [20, 35,36,42], in other studies, oral preparation was used. In all trials in which topical agents were used, cutaneous complications were reported as side effects [20,35,36,42].

Four trials mentioned that adverse effects were not related to the study product [23,25,28,34]. The most common side effects were gastrointestinal, dermatologic, and neurologic complaints. Gastrointestinal problems included diarrhea [26,27,29,32,33,39,41], nausea or vomiting [26,27, 30,39,43,44], acidity [40,41,44], constipation [31], abdominal pain or cramp [27,30,31,39,41,44], heartburn [24,39], dyspepsia [37], anorexia [26,29], and stomatitis [38]. Allergic and dermatologic complications were itching, burning sensation, and redness [20,31,36,39,42]. Neurologic problems were headache [22,30,39,43,74], insomnia [22,26], dizziness or vertigo [26,29,30], syncope [26], and violent behavior [31]. Table 1 shows the result of clinical trials that described the side effects of Boswellia consumption. In supplementary file 1, the severity of side effects according to clinical trials are described. As a result, there was not any severe adverse event in any of the reports.

Clinical trials reporting no side effect

Among the included studies, 27 indicated that Boswellia had no serious adverse effect [45-70,81], among

Table 1. Clinical trials of Boswellia mono-herbal preparations reporting side effects

Trial (Year)	Number Total (Boswellia)	Age (Gender)	Patient population	Preparation, dose, species	Treatment duration	SEs in Boswellia group (Number)	SEs in control group (Number)	Study design
Sander et al. (1998) [38]	37 (18)	19-70 (F, M)	Rheumatoid arthritis	Tab, three 400 mg thrice, *B. serrata*	12 weeks	Mild stomatitis (1) (1 case)	Moderate exanthema (1) Severe nausea (1) Joint pain increase (1) (3 cases)	RCT
Kimmatkar et al. (2003) [27]	30 (30)	> 40 (F, M)	Osteoarthritis	Cap, 333 mg thrice, *B. serrata*	8 weeks	Loose stool (1) Epigastric pain, nausea (1) (2 cases)	Not mentioned	RCT Cross-over
Sontakke et al. (2007) [41]	66 (33)	40-70 (F, M)	Osteoarthritis	Cap, 333 mg thrice, *B. serrata*	6 months	Acidity (3) Diarrhea, cramp (1) (4 cases)	Acidity (2) (2 cases)	RCT
Sengupta et al. (2008) [39]	75 (50)	40-80 (F, M)	Osteoarthritis	Cap, 50 mg/125 mg twice, *B. serrata*	90 days	Diarrhea, nausea, vomiting, abdominal pain, stomach burn (18) Allergy, itching (6) Headache (1) Fever (4) Weakness (6) Edema (1) Body pain, loss of hair, chest pain, eye infection (8) (Numbers of adverse events)	Diarrhea, nausea, vomiting, abdominal pain, stomach burn (13) Allergy, itching (5) Fever (1) Weakness (2) Body pain, loss of hair, chest pain, eye infection (9) (Numbers of adverse events)	RCT
Sengupta et al. (2010) [40]	60 (40)	40-80 (F, M)	Osteoarthritis	Cap, two 50 mg twice, *B. serrata*	90 days	Acidity (1) (1 case)	Acidity (1) (1 case)	RCT
Vishal et al. (2011) [43]	60 (30)	40-80 (F, M)	Osteoarthritis	Cap, 50 mg twice, *B. serrata*	30 days	Nausea, headache (1) (1 case)	Nausea, headache (1) (1 case)	RCT
Razavi et al. (2019) [35]	154 (51)	18-80 (F, M)	Osteoarthritis	Oil, 10 drop twice, *B. sacra (B. carteri)*	6 weeks	Itching (1) (1 case)	No side effect	RCT
	130 (32)	40-75 (F, M)	Osteoarthritis	Tab, two 12.5 % twice, *B. serrata*	8 weeks	Constipation, diarrhea, and heartburn (21) (Not related to Boswellia)	Constipation, diarrhea, and heartburn (21) (Not related to Boswellia)	RCT
Gerhardt et al. (2001) [23]	102 (50)	18-70 (F, M)	Crohn's disease	Tab, three 400 mg thrice, *B. serrata*	8 weeks	Infection (7) Fatigue (1) (Not related to Boswellia)	Infection (13) Headache (2) Intestinal cramps, abdominal pain and vomiting (1) Vomiting, dizziness and physical weakness (1) (Not related to Boswellia)	RCT
Gupta et al. (2001) [24]	30 (20)	18-48 (F, M)	Chronic Colitis	Cap, 300 mg thrice, *B. serrata*	6 weeks	Heartburn (2) (2 cases)	No side effect	NRS

Madisch et al. (2007) [29]	31 (16)	18-80 (F, M)	Collagenous colitis	Cap, 400 mg thrice, *B. serrata*	6 weeks	Dizziness, hypoglycemia, loss of appetite (1) Diarrhea, enteritis (1) (2 cases)	Eczema, coxsackie virus infection (1) (1 case)	RCT
Holtmeier et al. (2011) [25]	82 (42)	18-75 (F, M)	Crohn's disease	Cap, two 400 mg thrice, *B. serrata*	52 weeks	Infection (17) Gastrointestinal (15) Nervous system (6) Musculoskeletal (5) Investigations (4) Skin (4) General disorders (3) Psychiatric disorders (2) Immune system (2) Blood disorders (1) (Not related to Boswellia)	Infection (16) Gastrointestinal (20) Nervous system (3) Musculoskeletal (7) Investigations (9) Skin (6) General disorders (6) Psychiatric disorders (1) Blood disorders (1) (Not related to Boswellia)	RCT
Belcaro et al. (2017) [21]	71 (24)	36.0 ± 3.0 (F, M)	Irritable bowel syndrome	Tab, 250 mg once, *B. serrata*	4 weeks	Mild stypsis (2) (2 cases)	Nausea (2) Nausea, headache (4) Hypotension (2) (8 cases)	NRS
Kirste et al. (2011) [28]	40 (20)	32-83 (F, M)	Cerebral edema	Cap, Four 350 mg thrice, *B. serrata*	1 week	Nausea (6) Vomit (2) Dizziness (6) Diarrhea (6) (Not related to Boswellia)	Nausea (4) Vomit (1) Dizziness (3) Seizure (1) (Not related to Boswellia)	RCT
Moein et al. (2013) [31]	38 (38)	15-65 (F, M)	Diffuse axonal injury	Cap, 360 mg thrice, *B. serrata*	6 weeks	Abdominal pain (1) Constipation (1) Skin macula (1) Violent behavior (1) Dim vision (1) Dark urine (1) (6 cases)	Diarrhea (2) Dim vision (1) Renal impairment (1) (4 cases)	RCT
Rezakhani et al. (2020) [37]	120 (60)	55-85 (F, M)	Dementia	Cap, 300 mg/kg, twice, *B. serrata*	12 weeks	Dyspepsia (1) (1 case)	Dyspepsia (1) (1 case)	RCT
Meshkat et al. (2022) [30]	80 (46)	***36.70 ± 15.2*** (F, M)	Traumatic brain injury	Tab, 400 mg thrice, *B. serrata*	12 weeks	Headache (5) Abdominal pain (1) Dizziness (3) Nausea (2) Vertigo (1) (Side effects number)	Headache (1) (1 case)	RCT
Karima et al. (2023) [26]	85 (43)	***60-85*** (F, M)	Alzheimer's Disease	Cap, 400 mg thrice, *B. serrata*	6 months	Diarrhea (1) Anorexia (4) Fatigue (4) Insomnia (3) Asthenia (1) Dizziness (1) Orthostatic hypotension (2) Nausea (6) Leg cramp (2) Syncope (1) (Side effects number)	Diarrhea (1) Anorexia (2) Insomnia (3) Asthenia (1) Dizziness (3) Nausea (2) Vomiting (1) (Side effects number)	RCT
Togni et al. (2015) [42]	114 (55)	32-78 (F)	Mammary carcinoma	Cream, 2% twice, *B. serrata*	Radiation days	Itching, burning (21) (21 cases)	Itching, burning (29) (29 cases)	RCT

Pasta et al. (2015) [33]	62 (32)	22-51 (F)	High breast density	Cap, two 50 mg twice, Not mentioned	6 months	Diarrhea (1) (1 case)	No side effect	RCT
Pasta et al. (2016) [32]	62 (32)	22-51 (F)	Mastalgia Breast lump	Cap, two 50 mg twice, Not mentioned	6 months	Diarrhea (1) (1 case)	No significant adverse effects	RCT
Gupta et al. (1998) [44]	80 (40)	18-75 (F, M)	Asthma	Gum resin, 300 mg thrice, *B. serrata*	6 weeks	Stomach pain, hyperacidity, nausea (2) (2 cases)	Not mentioned	RCT
Ferrara et al. (2015) [22]	32 (18)	18-80 (F, M)	Asthma	Tab, 500 mg once, *B. serrata*	4 weeks	Headache (5) Insomnia (3) (8 cases)	Headache (5) Insomnia (1) Nausea (2) Constipation (3) (11 cases)	RCT
Reis el al. (2023) [36]	70 (35)	>18 (F, M)	Cancer- related fatigue	Oil 5%, on sole and feet *B. carteri*	2 days before chemotherapy to 2 days after it for 2 cycles	Dermatitis (1) (1 case)	No side effect	RCT
Badr et al. (2023) [20]	54 (28)	20-60 (F, M)	Second-degree Burn Wounds	Cream 40 % *B. carteri*	Until complete healing	Hypersensitivity (4) (4 cases)	Infection (1) (1 case)	RCT

F: Female, M: Male RCT: Randomized clinical trial NRS: Non-randomized study

them two studies were crossover [62,67]. Total of 845 subjects in the Boswellia group tolerated it well. The age of the patients who participated in these studies was between a minimum of 15 [59, 66] and a maximum of 80 years old [47,57].

Knee osteoarthritis [47,53,55,57,58 64] was the most prevalent disease in these investigations. Three studies were about diabetes mellitus [45,46,56], two on oral cavity diseases [63,66], two on healthy volunteers [62,67], and one trial on each of the other diseases, as mentioned in table 2.

The species used was *B. serrata* in 23 studies [45, 46, 50-70] and *B. carteri* in three studies [48, 49,81]; one study did not mention the species [47]. The shortest treatment period was a single dose [62,67], and the longest was 6 months [59, 65]. In 20 studies, the oral form of Boswellia was used [45-47,50-56,58,59,61,62,64-67,69,70]. In four studies topical agents were used [57,60,68,81], in one study mouthwash [63], oil on gauze [48], and Sitz-bath were used respectively [49]. Minimum oral daily dose was 7.2 mg [58] and the maximum dose was 3 g [70]. (Table 2)

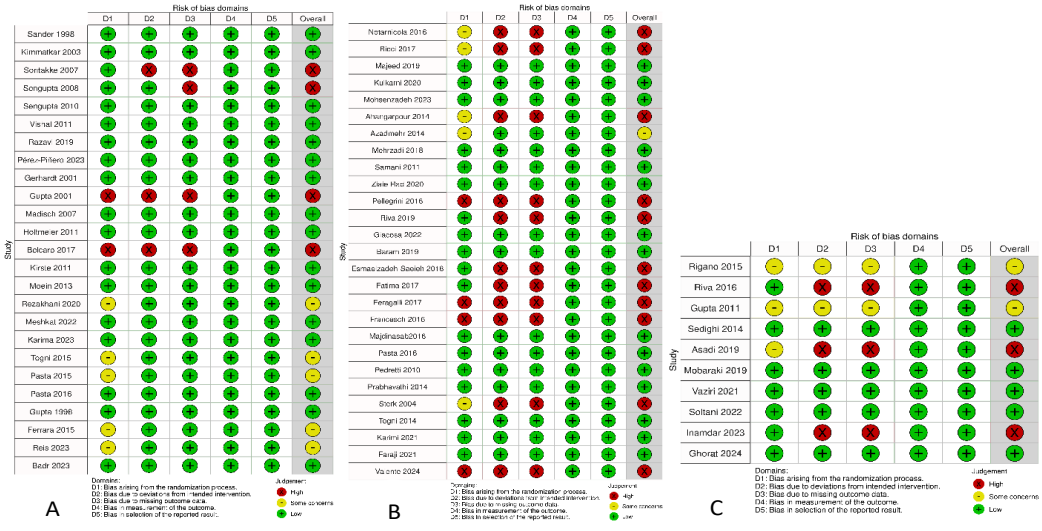


Figure 4. Risk of bias summary (RoB2); RoB2 of Table 1 (A), RoB2 of Table 2 (B), RoB2 of Table 3 (C), D: Domain

osteoarthritis [73], nipple pain during breast feeding [75], pressure ulcers [80], aphthous ulcers [79], vulvovaginal Candidiasis [74], and Alzheimer's disease [72]. Also, three studies were done among healthy volunteers [76,77] and the elderly men [71]. Five articles used *B. serrata* [73,74,76,77,79], one study used *B. carteri* [80], and one study used *Boswellia papyrifera* [78]. Three studies did not mention the species [71,72,75]. Duration of Boswellia consumption was between single dose [77] and 18 weeks [72]. Oral dose of Boswellia ranged from 300 mg [72,78] to 1500 mg daily doses [73]. (Table 3)

RoB assessment

RoB of 62 included clinical trials was assessed. The summary of the RoB2 results is provided in Figure 4. 69.3 % (43/62 studies) had appropriate randomization. About 9.6 % (6/ 62 studies) had high risk selection bias, and other clinical trials rated as some concerns. In about 30 % of included trials blindness rated as high risk. Attrition and reporting of outcomes were acceptable in the included studies.

Case reports

We evaluated 10 case reports [82-91]. No case series were enrolled according to inclusion criteria. One report was from a male [87] and others from females [82-86,88-91]. All of them had underlying diseases [82-91] except one [85]. The youngest case was a 13-year-old girl who had no underlying diseases and developed hypersensitivity pneumonitis and prolonged recurrent pneumonia with Boswellia overuse; she was successfully treated with systemic corticosteroids and quit the consumption of the plant [85]. Another young case was a 17-year-old female with celiac who developed bezoar because of excessive olibanum intake and improved with surgical removal of bezoar [84]. The oldest case had a previous medical history of dermatitis and had contact dermatitis with Boswellia as well [83]. The most prevalent side effect was cutaneous complication reported in 5 people [82,83,89-91]. First, a 28-year-old female with atopy reported allergic contact dermatitis with a cream containing *B. serrata* for the first time after 5 days of application, and an intense eczematous local cutaneous reaction

Table 2. Clinical trials of Boswellia mono-herbal preparations reporting no side effect

Trial (Year)	Number Total (Boswellia)	Age (Gender)	Patient population	Preparation, dose, species	Treatment duration	Study design
Notarnicola et al. (2016) [58]	120 (60)	59.2 ± 13 (F, M)	Osteoarthritis	Sachet, 3.6 mg twice, *B. serrata*	60 days	RCT
Ricci et al. (2017) [64]	60 (30)	40-70 (F, M)	Osteoarthritis	Tab, 100 mg once, *B. serrata*	20 days	RCT
Majeed et al. (2019) [55]	48 (24)	35-75 (F, M)	Osteoarthritis	Tab, 169.33 mg twice, *B. serrata*	120 days	RCT
Kulkarni et al. (2020) [53]	45 (45)	> 18 (F, M)	Osteoarthritis	Tab & Cap thrice, *B. serrata*	2 months	RCT
Mohsenzadeh et al. (2023) [57]	90 (45)	40-80 (F, M)	Osteoarthritis	Topical oily solution thrice, *B. serrata*	4 weeks	RCT
Ahangarpour et al. (2014) [45]	60 (30)	30-48 (F, M)	Diabetes mellitus	Resin, 300 mg thrice, *B. serrata*	6 weeks	RCT
Azadmehr et al. (2014) [46]	71 (37)	18-65 (F, M)	Diabetes mellitus	Cap, 400 mg twice, *B. serrata*	12 weeks	RCT
Mehrzadi et al. (2018) [56]	56 (27)	18-65 (F, M)	Diabetes mellitus	Resin, 250 mg twice, *B. serrata*	8 weeks	RCT
Samani et al. (2011) [66]	74 (49)	15-18 (F)	Gingivitis	Extract, 0.1 g thrice, Or Powder, 0.2 g thrice, *B. serrata*	14 days	RCT

Ziaie Rad et al. (2020) [63]	90 (45)	18-38 (F, M)	Mechanical ventilated (Dental plaque)	Mouthwash, twice, *B. serrata*	4 days	RCT
Pellegrini et al. (2016) [61]	43 (22)	52.1 ± 2.2 (F, M)	Ulcerative colitis	Tab, 250 mg once, *B. serrata*	4 weeks	NRS
Riva et al. (2019) [65]	69 (35)	45.1±1.2 (F, M)	Irritable bowel syndrome	Tab, 250 mg once, *B. serrata*	6 months	RCT
Giacosa et al. (2022) [52]	49 (24)	18-70 (F, M)	Acute Diarrhea	Tab, 250 mg twice, *B. serrata*	5 days	RCT
Baram et al. (2019) [47]	80 (41)	40-80 (F, M)	Ischemic stroke	Cap, two 400 mg thrice, Not mentioned	4 weeks	RCT
Esmaelzadeh-Saeieh et al. (2018) [48]	126 (63)	20-40 (F)	Nulliparous women	Oil on gauze, 0.2 mL, *B. carteri*	every 30 min up to a cervical dilation of 10 cm	RCT
Fatima et al. (2017) [70]	48 (16)	20-60 (F, M)	Obese adults	Powder, 3 g once, *B. serrata*	8 weeks	RCT
Feragalli et al. (2017) [50]	72 (35)	32.5±2.4 (F, M)	Ankle sprain	Tab, 250 mg once, *B. serrata*	7 days	NRS
Francesch et al. (2016) [51]	52 (25)	18.3±4.3 (M)	Rugby players with knee pain	Tab, two 250 mg 5 days, followed by 250 mg 23 days once, *B. serrata*	4 weeks	NRS
Majdinasab et al. (2016) [54]	60 (30)	16-53 (F, M)	Multiple sclerosis	Cap, 450 mg twice, *B. serrata*	2 months	RCT
Pasta et al. (2016) [59]	64 (36)	15-30 (F)	Fibroadenoma	Cap, two 50 mg twice, *B. serrata*	6 months	RCT
Pedretti et al. (2010) [60]	15 (15)	31-68 (F)	Photo and age-damaged skin	Cream, 0.5 % once, *B. serrata*	1 month	RCT
Prabhavathi et al. (2014) [62]	12 (12)	18-45 (M)	Healthy volunteers	Cap, two 125 mg once, *B. serrata*	Single dose	RCT Cross-over
Sterk et al. (2004) [67]	12 (12)	24 -39 (M)	Healthy volunteers	Cap, three 262 mg once, *B. serrata*	single dose	RCT Cross-over
Togni et al. (2014) [68]	59 (19)	27.3- 51.5 (F, M)	Psoriasis and eczema	Cream, twice, *B. serrata*	30 days	RCT
Karimi et al. (2021) [81]	36 (18)	18-65 (F, M)	Carpal tunnel syndrome	Oleogel, 1.5 fingertips twice, *B. carteri*	6 weeks	RCT
Faraji et al. (2021) [49]	90 (30)	18-41 (F)	Episiotomy wound	Sitz-bath, 20 mL extract 10 min twice, *B. carteri*	1 week	RCT
Valente et al. (2024) [69]	38 (20)	≥ 18 (F)	Breast cancer	Cap, two 400 mg thrice, *B. serrata*	5-23 days	NRS

F: Female, M: Male RCT: Randomized clinical trial

Table 3. Clinical trials of Boswellia mono-herbal preparations with no report of side effects

Trial (Year)	Number Total (Boswellia)	Age	Patient population	Preparation, dose, species	Treatment duration	Study design
Rigano et al. (2015) [76]	30 (30)	18-60 (F, M)	Healthy volunteers	Emulsion, 1% twice, *B. serrata*	1 week	RCT
Riva et al. (2016) [77]	12 (12)	20-51 (F, M)	Healthy volunteers	Cap, 500 mg once, *B. serrata*	Single dose	RCT Cross-over
Gupta et al. (2011) [73]	56 (29)	40-70 (F, M)	Osteoarthritis	Cap, four 500 mg thrice, *B. serrata*	2 months	RCT
Sedighi et al. (2014) [78]	80 (40)	36.58 ± 8.50 (F, M)	Multiple sclerosis	Cap, 150 mg twice, *B. papyrifera*	2 months	RCT
Asadi et al. (2019) [71]	20 (12)	60.2 ± 1.7 (M)	Elderly men	Cap, 500 mg twice, Not mentioned	4 weeks	RCT
Mobaraki et al. (2019) [75]	68 (34)	----- (F)	Nipple pain during breast feeding	Ointment, 2 % twice, Not mentioned	1 week	RCT
Vaziri et al. (2021) [80]	75 (25)	> 18 (F, M)	Pressure ulcers	Gel 5 % *B. carteri*	5 weeks	RCT
Soltani et al. (2022) [79]	81 (41)	> 18 (F, M)	Aphthous ulcers	Tab, 200 mg quartan, *B. serrata*	3 days	RCT
Inamdar et al. (2023) [74]	40 (20)	18-45 (F)	Vulvovaginal Candidiasis	Tab vaginal, 1 g bed time, *B. serrata*	3 weeks	RCT
Ghorat et al. (2024) [72]	72 (36)	50-75 (F, M)	Alzheimer disease	Chewing gum, 20 min,100 mg thrice, Not mentioned	18 weeks	RCT

with bullae developed on her thigh. Some months later, she applied the same cream to her husband for muscle pain and developed dermatitis again. Her lesion healed with topical and systemic corticosteroid [82]. The second case was a 36- year-old female with a burn that developed dermatitis in the thigh by *B. sacra (B. carteri*) ointment. She was improved with topical corticosteroid and vitamin A&D [91]. The third dermatologic complication was sweet syndrome in a 58-year-old female, a case of Crohn's disease and rheumatoid arthritis [90]. Forth, the case showed allergy to frankincense proved with a patch test, but her final outcome was not described; in other cases, complications improved finally with different approaches. Finally, a 45-year-old female used several herbal medicines for her pain. When she had significant dermatitis, a patch test was done and allergy to Boswellia was determined [89].

A useful effect was a decrease in blood sugar in a 60-year-old female with pancreatic cancer as it resulted in a decrease in the required insulin dose for the patient [88]. (Table 4)

Spontaneous reporting schemes

World health organization report

World Health Organization (WHO) collaborating center for the International Drug Monitoring Database mentioned 15 side effect reports for *B. serrata* and 10 reports for *B. carteri* (*B. sacra*) from 2004 to 2024. It was not explained that these reports were related to multi-herbal medications or just Boswellia. Eight cases were from America, 15 from Europe, and two from Asia. Their age ranged from 12 to over 75 years old. Fifteen cases were female, nine were male, and the gender of one case was not reported. General disorders and administration site disorders, and skin and subcutaneous disorders were the most prevalent adverse events. The detailed information about the side effects of Boswellia reported by WHO is summarized in supplementary file 2.

Canadian Vigilance Adverse Reaction Online Database

It has reported two cases, both of which used combined drugs, and there is no single report related to Boswellia.

Australian Database of Adverse Event Notifications (DAEN)

From January 1971 to May 2024, the Australian Database of Adverse Event Notifications (DAEN) received adverse effects with medications that contained just

Table 4. Case reports of Boswellia

Study (Year)	Age and Gender	Health status	Exposure	Side effects	Outcome
Acebo et al. (2004) [82]	28 F	Atopic background had a 2nd degree burn	Naturopathic cream, including *B. serrata* extract for 5 days	Allergic contact dermatitis	Healed with systemic and topical corticosteroids
Badr et al. (2018) [91]	36 F	Burn wounds because of hot oil	*B. sacra (B. carteri)* 40% ointment for 13 days	Erythema, exudation, papules, flaking, itching on her thigh with deep 2nd degree Burn	Topical corticosteroid and vitamin A&D ointment was prescribed for treatment
Buonomo et al. (2021) [83]	68 F	Eczema	Frankincense oil *(B. carteri)* for 4 days	Allergic contact dermatitis according to patch teste	Not mentioned
El Fortia et al. (2006) [84]	17 F	Celiac	Large quantities olibanum, repeatedly	olibanum bezoar	Treated surgically and the bezoar removed through a vertical gastrostomy incision
Lukoseviciute-Zike et al. (2015) [85]	13 F	No underlying disease	Frankincense overuse	Prolonged and recurrent respiratory infection, pneumonia	Successfully treated with systemic corticosteroids
O'Connor et al. (2014) [87]	61 M	Occupational asthma	Fumes from burning incense	Cough, dyspnea and wheeze	Intermittent cough and dyspnea on exposure to multiple other sources
Reis et al. (2018) [88]	60 F	Pancreatic cancer	1-2 drop frankincense essential oil 5% bid, on sole of both foot for several days before, during and after chemotherapy	Blood sugar decreased	Insulin dose decreased
Wagner et al. (2019) [90]	58 F	Crohn and rheumatoid arthritis	Incense capsule	Sweet syndrome, itching, aching, red blister on the torso and on the distal phalanges	Healed with systemic steroid therapy over several weeks
Tsimpidakis et al. (2020) [89]	45 F	Use aromatherapy for pain	Frankincense essential oil (B. carteri)	Patch test revealed a very strong positive reaction	Dermatitis cleared after topical treatment with steroids
Mejía et al. (2021) [86]	23 F	Polycystic ovarian syndrome	Homeopathic cream based on *B. serrata* for joint pains in knee and shoulders for 3 months	Exogenous Cushing Syndrome	With the drug's suspension clinical findings have improved, and cortisol levels have decreased

F: Female, M: Male

Boswellia in one case. It was jaundice with abnormal liver function test.

Discussion

Herbal medicines are not completely safe [13]. Overdose of them may cause poisoning, life-threatening complications, and death. Therefore, it is a fundamental principle to mention the safety of herbal drugs [92]. However, their complications are under-reported in comparison with conventional drugs. There are several systematic reviews about the efficacy of Boswellia in different diseases [4,11,93], but its side effects were not systematically reviewed.

In this study, we reviewed several investigations on humans, associated with the use of Boswellia mono-herbal preparation. These include clinical trials,

case reports, and spontaneous reporting schemes. In 40.3% of clinical trial studies, Boswellia consumption was associated with adverse effects. The most reported adverse effects from oral consumption of Boswellia were related to gastrointestinal problems including diarrhea, nausea and vomiting, abdominal pain, and acidity, and from topical use including itching, burning sensation, and redness. 43.5% of the eligible clinical studies in this systematic review reported that Boswellia was well tolerated by study participants and was not associated with adverse events. Among 62 clinical trials, 10 studies had not mentioned any data about the side effects of Boswellia [71-80]. Hamid Zare et al. (2022) in a systematic review of pomegranate mentioned that 16.6 % of included clinical trials reported side effects including gastrointestinal problems, flu-like symptoms, and urinary problems. Furthermore, in about a third of studies it was introduced as a safe fruit and 51.5 % of studies have not mentioned any adverse effects [94]. In Hajimonfarednejad et al. (2018) survey about the side effects of cinnamon 50% of included in clinical trials have not declared complications as well [13].

Not reporting side effects may be because evaluation of the efficacy of a plant in the treatment of diseases was more important than detection of its side effects. In addition, it may be related to ignoring appropriate monitoring tools, hiding some of the data, or not paying attention to the importance of side effects of herbal remedies [94]. Researchers should become familiar with herbal toxicities and have planned to identify them before starting their research [95]. For accuracy in reporting side effects, the researcher can design a questionnaire for adverse events and in the follow-up of the patients, in addition to evaluating response to treatment, ask questions about complications. The most prevalent complications in the trials of our study were gastrointestinal disorders that were not life-threatening. In studies with Boswellia consumption, some complications mentioned in adverse effects may occur due to underlying diseases [25,28,34]. Thus, determining the causality of adverse events in the studies is important [95]. Investigations on healthy volunteers while considering ethical principles help to distinguish the complications directly related to Boswellia.

Traditionally, *B. serrata* and *B.carteri* have been used for the treatment of many diseases [11]. Our study determined that the most prevalent species of Boswellia in clinical trials was *B. serrata.*

Most case reports published about Boswellia were about its efficacy [88,96,97]; also, Boswellia was used in multi-herbal medications [98-100]. We found 10 cases with side effects associated with the use of Boswellia mono-herbal preparation. Cutaneous complications were the most frequent type of side effects between them [82,83,89-91].

Case reports are important because they warn about unexpected complications that may be life-threatening [101, 102]. We should pay attention to these side effects because some complications do not improve without surgical or medical interventions [84,85]. Some adverse events occur because of herbal abuse or the fact that patients have no information about the side effects of the herbs or drug-herb interactions [103]. Therefore, the incidence of side effects in case reports provides the practitioner with some insights to give more information to patients.

WHO Collaborating Center for International Drug Monitoring Database did not mention a detailed formulation of the medication. Today, an acceptable safety profile of herbal products is necessary [104, 105], and to achieve this goal, it is suggested that in studies, in addition to effectiveness, researchers should consider their side effects. It is also necessary to have evidence-based data-gathering research for assessing adverse events [106]. Also, due to the increasing use of medicinal plants in all countries of the world, including developing countries, it is necessary to further apply the spontaneous reporting systems in these countries as well [107].

Conclusions

The available data suggested that Boswellia was well tolerated in most people and had no life-threatening complication, but it might have side effects that may require treatment to be resolved, especially gastrointestinal disturbance and allergic reactions; therefore, its consumption should be monitored, probable side effects should be described for patients, and it should not be considered completely safe.

Ethical Considerations

The study was approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.sums.med.rec.1399.130)

Conflict of Interests

All the authors have no conflict of interest to declare.

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Supplementary file 1. Description of side effects severity in the trial

Trial (Year)	Boswellia tolerability
Sander et al. (1998) [38]	A mild stomatitis occurred, which stopped after a break in therapy and not recur after re-exposure
Kimmatkar et al. (2003) [27]	Responded to usual symptomatic treatment. None of these two patients discontinued the drug because of the adverse effects. General patient compliance to BSE was satisfactory.
Sontakke et al. (2007) [41]	No severe side effects. They responded to treatment with tablet ranitidine 150 mg twice daily for seven days and chose to continue with the trial
Sengupta et al. (2008) [39]	Some minor adverse events were noted. Did not reveal any major adverse effect. It is safe for human consumption
Sengupta et al. (2010) [40]	No major adverse effect. Safe for human consumption
Vishal et al. (2011) [43]	No major adverse effect. the study validates the safety of Aflapin
Razavi et al. (2019) [35]	This study demonstrates the potential efficacy and safety of oliban oil with only minor local skin pruritus
Pérez-Piñero et al. (2023) [34]	Adverse events of mild intensity and unrelated to the study product
Gerhardt et al. (2001) [23]	Adverse events recorded after treatment with H 15 show no clear casual connection with the study medication
Gupta et al. (2001) [24]	Minimal side effect
Madisch et al. (2007) [29]	Was well tolerated, and no serious adverse events were reported
Holtmeier et al. (2011) [25]	Adverse events were not related to the study medication. The trial confirmed good tolerability of a new Boswellia serrata extract
Belcaro et al. (2017) [21]	Casperome® supplementation was related to a lower incidence of side effects
Kirste et al. (2011) [28]	No adverse effect associated with the *B. Serrata.* Two patients had grade 3 and 4 toxicity, both of whom were in the placebo group
Moein et al. (2013) [31]	The reported adverse events were all of mild quality
Rezakhani et al. (2020) [37]	Two patients from both groups dropped out of study due to dyspepsia
Meshkat et al. (2022) [30]	No Boswellia-related serious adverse events were reported and no side effects required medical attention. Patients in Boswellia group reported only minor, temporary and reversible treatment related adverse effects
Karima et al. (2023) [26]	Regimen was well tolerated, safe, and efficacious. No serious adverse events reported
Togni et al. (2015) [42]	No severe adverse effects. Could be safely applied
Pasta et al. (2015) [33]	No significant adverse effects
Pasta et al. (2016) [32]	No significant adverse effects
Gupta et al. (1998) [44]	Adverse effects of *B. serrata* were minor
Ferrara et al. (2015) [22]	Good safety profile
Reis el al. (2023) [36]	Only 1 adverse event was recorded for our study (redness, swelling, and pain of the feet and hands) that was managed by stopping the oil application.
Badr et al. (2023) [20]	The likelihood of contact dermatitis with *Boswellia* should be taken into consideration

Supplementary file 2. World health organization report

Side effect	Age group	sex
Blood and lymphatic system disorders (2)	12-17 (1)	Female (15)
Cardiac disorders (4)	18-44 (3)	Male (9)
Gastrointestinal disorders (3)	45-64 (6)	Unknown (1)
Hepatobiliary disorders (1)	65-74 (8)	
General disorders and administration site conditions (12)	>75 (2)	
Injury, poisoning and procedural complications (3)	Unknown (5)	
Investigations (7)		
Musculoskeletal and connective tissue disorders (2)		
Neoplasms benign, malignant and unspecified (1)		
Nervous system disorders (5)		
Psychiatric disorders (4)		
Renal and urinary disorders (1)		
Respiratory, thoracic and mediastinal disorders (1)		
Skin and subcutaneous tissue disorders (9)		
Vascular disorders (2)		
Eye disorder (1)		
Infections and infestations (1)		
Immune system disorders (1)		
Metabolism and nutrition disorders (2)		

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