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Cancer Chemopreventive Effects of *Boswellia sacra* Gum Resin Hydrodistillates on Invasive Urothelial Cell Carcinoma: Report of a Case

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Abstract

A 52-year-old Hispanic male presented with hematuria and was later diagnosed with a large invasive high-grade urothelial cell carcinoma (UCC) of the urinary bladder, but with ambiguous pT1/pT2 staging regarding musclaris propria invasion by UCC. The conventional treatment including radical cystoprostatectomy followed by neoadjuvant chemotherapy with or without radiation therapy was presented. The patient decided to delay the standard therapy until a later stage, but elected to go through transurethral resection of bladder tumor (TURBT) without Bacillus Calmette-Guérin instillation. Following TURBT, the patient started oral *Boswellia sacra* gum resin (aka frankincense or Ru Xiang in Chinese) hydrodistillates (BSGRH) administration at 3 mL daily with lifestyle changes, and continued this regimen in the last 25 months. Within the first year after diagnosis, the patient experienced 2 recurrences. Recurrent tumors were removed by TURBT alone and both tumors were far smaller than the original one. After the second recurrence, the patient has no detectible cancer in the bladder based on cystoscopy for 14 months and has an intact genitourinary system. His liver and kidney functions are considered to be normal based on blood chemistry tests. This index case suggests that BSGRH may have cancer chemopreventive effects on UCC. The use of *Boswellia*-derived products in the management of cancer has been well document in other published studies, and boswellic acids have been suggested to be the major component. However, BSGRH contains very little boswellic acids. Demonstration of cancer chemoprevention using BSGRH is one step forward in isolating the key components other than boswellic acids in frankincense. The critical question as to whether these components can simultaneously activate multiple pathways in cancer cells to execute cancer suppression/cytotoxicity or prevention effects remains to be addressed. More studies including identification of key molecules, pharmacokinetics of major compounds, as well as long-term benefits and possible adverse effects will be needed to meet the guidelines of the US Food and Drug Administration for botanical drug development.

Keywords

Boswellia sacra gum resin, frankincense, hydrodistillate, Ru Xiang, urothelial cell carcinoma, urinary bladder cancer

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Introduction

Urothelial cell carcinoma (UCC) of the urinary bladder is a common carcinoma among adults with an estimated 76 960 new cases and 16 390 deaths in the United States in 2016. Prognosis and treatment strategy of UCC are often dictated by a tumor's histologic grade and pathologic staging. While UCC without invasion or with invasion limited to the lamina propria are amenable to transurethral resection of bladder tumor (TURBT) and Bacillus Calmette–Guérin (BCG) vaccine treatment, UCC with invasion into the muscularis propria (detrusor smooth muscle) often requires radical

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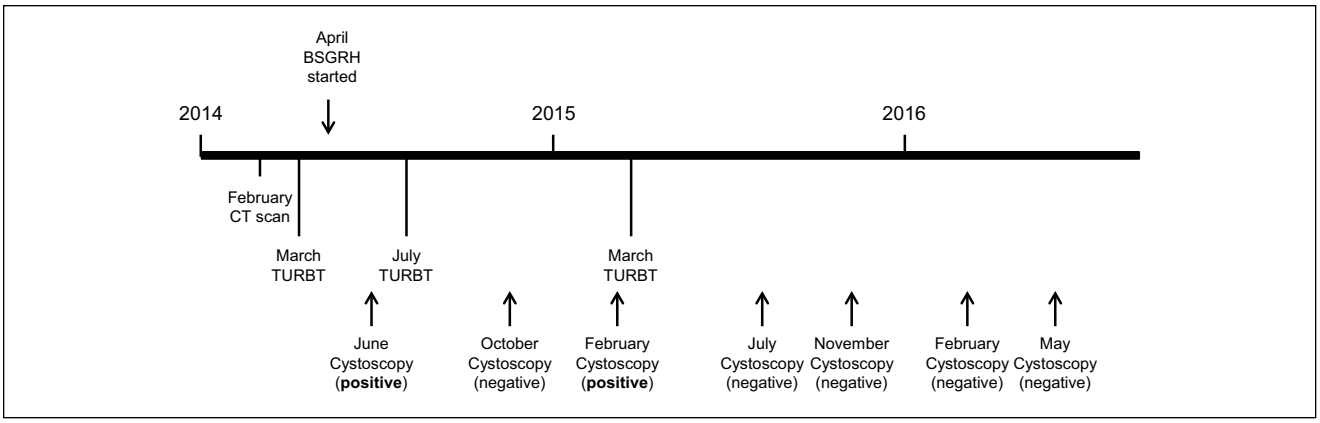

Figure 1. Timeline of events.

cystectomy in females and radical cystoprostatectomy in males for successful treatment.

Standard radical cystoprostatectomy removes the entire bladder along with the prostate and seminal vesicles, and it is often accompanied by bilateral pelvic lymph node dissection to remove potential metastases in these lymph nodes. The patients would then receive either an ileal conduit or neobladder reconstruction to collect and drain the urine. After surgery and reconstruction, patients are recommended to receive neoadjuvant chemotherapy with or without radiation therapy for successful treatment. Although effective, this set of treatment is complicated, expensive, and leads to significant morbidity.

Frankincense (Ru Xiang in Chinese), a traditional Chinese and Ayurvedic herbal medicine, has been described to possess antitumor properties, in addition to its anti-inflammatory activity. Extracts prepared from gum resins of *Boswellia* species have been demonstrated to have anticarcinogenic activity in chemically induced mouse skin cancer models,[1] as well as antiproliferative and pro-apoptotic activities against rat astrocytoma cell lines[2] and in human leukemia cell lines.[3] Clinically, extracts from the resins have been shown to reduce the peritumoral edema in glioblastoma patients[2] and reverse multiple brain metastases in a breast cancer patient.[4] We previously reported that *Boswellia sacra* gum resin hydrodistillate (BSGRH), a form of extract of frankincense gum resins, possesses cancer cell–specific growth arrest and cytotoxicity in multiple types of human cancer cell lines in cultures,[5,6] suppresses tumor growth in a xenograft pancreatic cancer nude mouse model,[7] and simultaneously activates multiple pathways leading to cancer cell–specific death.[8] In this report, we describe cancer chemopreventive effects of oral BSGRH administration alone in a case of high-grade invasive papillary UCC during 2-year follow-up.

Case Presentation

The patient was a 52-year-old Hispanic male who self-detected gross hematuria and clots in urine between October and December of 2013. Contrast-enhanced computed tomography (CT) intravenous pyelogram (IVP) was first performed in February 2014 at Insight Imaging–Biltmore (Phoenix, AZ) and detected an irregular nonmobile mass of 4.2 × 4.3 × 3.7 cm around the right ureterovesical junction with thickening of adjacent bladder wall. There was no caliectasis or hydronephrosis, nor complications in upper tract collecting system or renal mass. The CT IVP image was strongly suggestive of a primary bladder neoplasia. In April 2014, fluoro-2-deoxy-D-glucose positron emission tomography/CT scan was performed at the University Medical Imaging at the University of Arizona Medical Center (Phoenix, AZ); and no distant metastasis was detected. The sequence of events is summarized in Figure 1.

TURBT was performed in March 2014 at St Joseph Hospital and Medical Center (Phoenix, AZ). The resected tumor was subjected to pathologic evaluation and staging. Endoscopic findings were suggestive of invasion of the muscularis propria. On pathologic examination, 2 different pathology groups expressed opposite opinions on whether there was genuine invasion of muscularis propria. While the initial pathology report made a diagnosis of invasive UCC with invasion of muscularis propria and thus corresponded to pT2 as per staging criteria of the American Joint Committee on Cancer, another pathology group made a diagnosis of a high-grade UCC with definitive invasion of the lamina propria but no definitive invasion of the muscularis propria corresponding to pT1 as per staging criteria of the American Joint Committee on Cancer.

Radical cystoprostatectomy followed by chemotherapy and/or radiation therapy was strongly recommended by 3 independent urologists who presided on this case. The patient declined cystoprostatectomy and any neoadjuvant chemotherapy/radiation therapy as well as BCG vaccine treatment along with TURBT, which would be a standard alternative in treatment of high-grade UCC. Instead, the patient chose to be followed-up regularly by cystoscopy and TURBT for recurrent tumors.

Table 1. Blood Markers for Liver and Kidney Functions.

Marker	March 2014	June 2014	September 2014	January 2015	April 2015	August 2015	March 16	Normal Range
AST	28	15	17	18	21	20	20	10-50 IU/dL
ALT	33	15	17	17	15	15	15	5-60 IU/L
Albumin	4.6	4.4	4.3	4.9	4.9	4.7	4.7	3.3-4.9 g/dL
Bilirubin	0.9	0.3	0.4	0.5	0.6	0.5	0.5	0.2-1.3 mg/dL
Creatinine	1.08	0.74	0.87	0.87	0.86	0.76	0.76	0.6-1.5 mg/dL
BUN	13	13	14	15	10	12	12	8-25 mg/dL
Total protein	6.8	6.6	6.7	7.1	7.1	6.9	6.9	6.0-8.0 g/dL

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen.

In late April 2014, the patient started oral administration of BSGRH at the dosage of 3 mL per day. The BSGRH was obtained from a commercial source and prepared by hydrodistillation of *Boswellia sacra* gum resins loaded into 55°C water with a ratio of 1:2.5 (w/v) and processed at 100°C for 24 hours as described previously.[6] Chemical profile of the BSGRH was determined and compared with those previously reported.[6,9] In addition, the patient made dietary changes by consuming more white meats versus red meats, taking vitamin C, organic multivitamins, broccoli sprout extract, and daily juicing (kale, carrot, ginger, parsley, apple, cucumber, and habanero), as well as practicing religious beliefs and regular exercises.

His first recurrence was detected in June 2014 during cystoscopy. A total of 20 tumors ranging from 0.2 to 3.0 cm were removed by TURBT, but no tumor was present in the original site. The second recurrence was discovered in February 2015, and TURBT was performed in March 2015 to remove a total of 6 lesions. No kidney involvement was observed. Regular cystoscopy surveillance was continued, and no new lesion had been detected as of the cystoscopy performed in May 2016 when this article was written. In the last 2 years, urinalysis was also conducted routinely along with cystoscopy and demonstrated the absence of abnormal activity. The patient had continued his daily oral dose of BSGRH during the entire course.

The patient reported the absence of any adverse effect from daily oral administration of BSGRH. Blood markers for liver functions including aspartate aminotransferase, alanine aminotransferase, albumin, and bilirubin were maintained within normal ranges. Levels of serum creatinine, blood urea nitrogen, and total protein monitoring kidney functions were also maintained within normal rages (Table 1). Blood chemistry test obtained in March 2014 before oral BSGRH administration was included as a reference.

Pathology

The initial TURBT specimen obtained in March 2014 yielded a 9.5 × 7.0 × 1.2 cm aggregate of tissue enough to fully fill 13 tissue cassettes. The specimen was composed exclusively of an invasive high-grade UCC (Figure 2A). The atypical epithelial cells formed a thick multilayer neoplastic proliferation (Figure 2B) with loss of polarity and many mitotic figures (Figure 2C). There were multifocal invasion of the lamina propria accompanied by significant desmoplastic reactions (Figure 2D) with necrosis present in some of these invasive foci (Figure 2E and F). There was no frank invasion of muscularis propria. However, there were some entrapped muscle fibers among tumor cells suggestive but not definitive of invasion of muscularis propria. This specimen had been examined by at least 3 different pathology groups (including KMF, coauthor of this article) and they expressed different opinions on whether there was definitive invasion of muscularis propria.

The second TURBT specimen (first recurrence) obtained in July 2014 yielded an aggregate of 2.0 × 2.0 × 0.8 cm tissue large enough to loosely fill 3 tissue cassettes. This specimen was composed exclusively of noninvasive papillary UCC. While about half of the tissue fragments had thick neoplastic epithelial lining, the other half had relative thin neoplastic lining that was limited to about 5 to 7 cells thick (Figure 2G and H). There was high-grade atypia and mitotic figures in both the thick and thin neoplastic epithelial layers (Figure 2I and J) although it is less mitotically active than the initial TURBT specimen.

The third TURBT (second recurrence) obtained in March 2015 yield a 1.0 × 1.0 × 0.3 cm aggregate of tissue enough to loosely fill 2 tissue cassettes. This specimen was composed exclusively of noninvasive papillary UCC (Figure 2K) with thickness of the neoplastic urothelial cells similar to the thinner ones from the second specimen (Figure 2L). In contrast to the previous 2 specimens, small mucin containing cysts were noted within the neoplastic epithelium (Figure 2M).

Discussion

With the initial diagnosis of high-grade aggressive pT1 UCC or possible pT2 invasive into the muscular propria, the case is considered to be potentially lethal. The standard

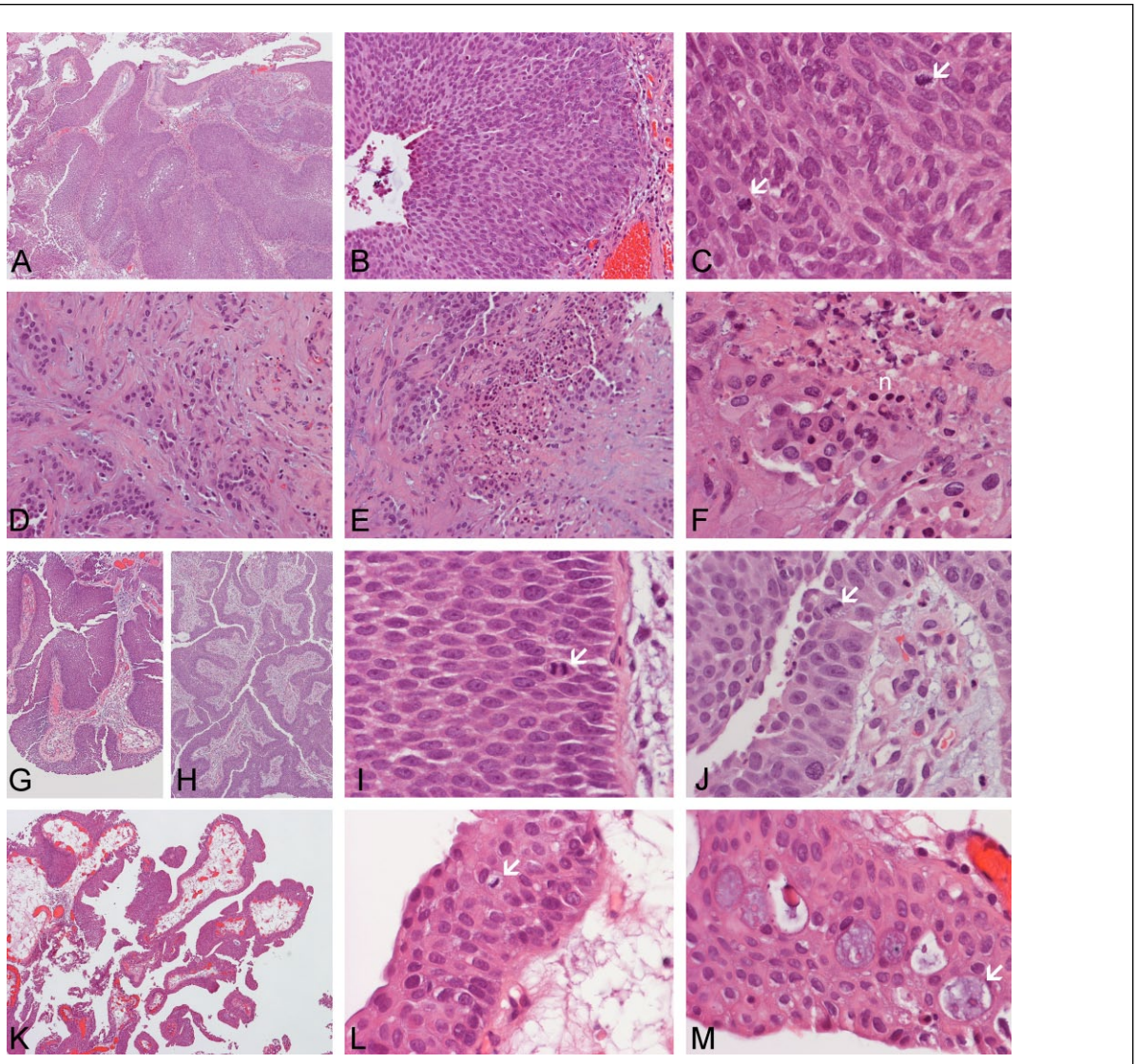

Figure 2. Pathology specimens obtained from the initial TURBT (A-F), first recurrence (G-J), and second recurrence (K-M). The first specimen consisted of high-grade papillary UCC (A) with thick layers of neoplastic epithelial proliferation (B), loss of polarity (C), and many mitotic figures (arrows in C). Definitive invasion of the lamina propria with desmoplastic changes (D) and focal necrosis (E and F) were present. The first recurrence consisted of noninvasive papillary neoplastic proliferation with thick (G) and thin (H) layers of neoplastic epithelial cells. Mitotic figures were present (arrows in I and J corresponding to areas with thick and thin neoplastic epithelium, respectively). The second recurrence consisted exclusively of noninvasive papillary UCC (K) with thin layers of neoplastic epithelial cells with occasional mitotic figures (L). Mucin-containing microcysts were noted in some of the neoplastic epithelium (M).

of care recommended by the 3 urologists who presided on this case was immediate radical cystoprostatectomy followed by neoadjuvant chemotherapy with or without radiation therapy. Instead, the patient elected to receive TURBT without BCG instillation.

TURBT alone was able to reduce tumor burdens immediately and made other regimens effective. With 2 incidences of recurrence within the first year following the initial tumor resection, this case suggested that the cancer was still active after TURBT. In the first recurrence, up to 20 small tumors were identified in a location separated from the original site and should be regarded as new primary tumors. This indicated that the tumorigenesis is still actively ongoing. The location of the second recurrence was not well documented, and it is difficult to conclude if this is a recurrent/residual tumor or new tumor. However, these 2 recurrent lesions were much smaller than the original tumor. The morphology was also different with a general tendency that the recurrent neoplastic epithelium was getting thinner and more organized as compared to the original tumor.

More studies will be required to understand the pathophysiological changes particularly at the molecular level in bladder cancer cells following BSGRH treatment. In addition, mucins are a family of polydisperse molecules, can be present in either secreted or membrane-associated form, and are part of the complex mucosal defense system.[10] Stojnev et al studied a correlation between multiple mucins and bladder cancer progression and reported that mucins 2 and 6 are associated with better overall survival, whereas mucin 1 expression may represent a more aggressive phenotype.[11] In this index case, a daily dose of 3 mL of BSGRH seems to have a cancer preventive effect as the patient is free of UCC in his urinary bladder in the last 14 months after the last recurrence as per cystoscopic surveillance. Also, since both recurrences occurred within the first 12 months after the initial TURBT, this raises a hypothesis that cancer chemopreventive effects of BSGRH probably builds up over a period of time, which then leads to 14 months tumor-free after the second recurrence.

The cancer community has been studying and promoting healthy lifestyles for cancer prevention and survival. Lifestyle factors including diet, nutritional supplements, exercise, and others have protective effects to reduce cancer risk. Studies suggest that increased consumption of red and processed meats is associated with higher cancer risk and cancer-related mortality in breast cancer,[12] pancreatic cancer,[13] and the upper aerodigestive tract cancer.[14] Healthy dietary patterns, including whole grains, vegetables, fruits, olive oil, and fish, seem to be more favorable for cancer prevention and prognosis. In addition, significant chemoprotective effects of higher fruit and vegetable consumptions have been described for breast cancer,[15] bladder cancer,[16] and colorectal cancer.[17] In contrast, other studies could not demonstrate cancer protective effect from fruit and vegetable consumption.[18] This discrepancy may be due to different mechanistic actions activated by biological compounds present in different fruits and vegetables.

Although inconsistent results have been obtained from many observational studies and clinical trials regarding the benefit of dietary supplements in cancer risk and survival, dietary supplements have been used in a large of portion of patients diagnosed with cancers.[19,20] Given the large number of cancer patients combining vitamins and herbs with conventional cancer treatments, more research is urgently needed to address issues related to possible synergistic benefits or adverse effects of herb-vitamin and drug-herb-vitamin interactions. More important, due to significant variations in dietary supplement formulation and manufacturing, the cancer community must improve patient-provider communication and offer reliable information to patients through appropriate research.

Many studies have consistently reported that increased physical activity in adults can reduce risk of developing multiple types of cancer. Morales-Oyarvide et al summarized that higher levels of physical activity are associated with lower overall and cancer-specific mortality in patients diagnosed with localized colorectal cancer.[21] Leach et al described that a longer duration exercise program may be beneficial to improve quality of life in breast cancer patients.[22] Exercise or physical activity is a safe, feasible, inexpensive, but effective intervention to improve cancer prognosis. Integrative approaches using conventional therapy along with lifestyle changes, dietary supplements, and exercise would significantly improve cancer survival.

The major group of chemical compounds in *Boswellia* species, boswellic acids, have been partially purified for treating arthritis based on their anti-inflammatory property.[23] In addition, boswellic acids have been studied for their anticancer activity in human cases.[4,24] However, we have to emphasize that boswellic acids may not be the active compounds presented in BSGRH due to the presence of very low high-molecular-weight boswellic acids in the hydrodistillate.[6] Demonstration of cancer chemoprevention using BSGRH is one step forward in identifying and isolating the key components other than boswellic acid from the *Boswellia* species. Furthermore, combinations of different chemical compounds may strengthen chemopreventive effects. Identification of biologically active compound(s) and study of possible synergistic effects of different constituents that provide chemopreventive benefits will be addressed in the future.

Extracts from gum resins of *Boswellia* species are considered to be relatively safe. For examples, 2 formulas of *Boswellia serrata* extracts were studied in rats and exhibited no detectible adverse effect. Oral administration of a *Boswellia serrata* extract containing 30% 3-O-acetyl-11-keto-β-boswellic acid (AKBA) at the dose of 1.5 g/kg/day in male and female Sprague-Dawley rats for 90 days did not result in abnormal changes based on hematology, clinical chemistry, and histopathological evaluations.[25] Another *Boswellia serrata* extract consisting of at least 20% AKBA also showed no observed adverse effect at greater than 2.5 g/kg body weight in Sprague-Dawley rats.[26] These extracts have been used in humans in clinical trials at the dose of 0.1 g/day and demonstrated safety and efficacy in the treatment of osteoarthritis of the knee.[10,27] In addition, oral administration of an alcoholic extract of *Boswellia ovalifoliolata* stem-bark to male Wistar albino rats at the dose of 0.5 g/kg for 28 days did not result in detectible abnormality.[28] In this report, the patient took the dose equivalent to 0.04 mL/kg body weight/day of the BSGRH with a relative density about 0.9. After 2 years of uninterrupted oral administration, all blood markers for liver and kidney functions remained within normal ranges.

Current development of pharmaceutical drugs has been largely based on the single compound-single pathway strategy. Combination drug therapy has been practiced in modern medicine for complicate diseases like AIDS and cancer

in order to simultaneously block multiple pathways to provide a higher efficacy. BSGRH contains more than 600 identifiable compounds.[6,7] The mixture of chemical constituents in BSGRH simultaneously activates many genes responsible for antiproliferative and pro-apoptotic effects through multiple signaling pathways in cancer cells.[8] More important, BSGRH, within a window of concentration, executes cancer cell–specific cytotoxicity in multiple types of human cancer cell lines.[5,6] Isolation and purification of a single compound from frankincense extracts may not be as effective as crude extracts for the intended therapeutic purpose due to complexity of chemical profiles and possible synergistic effects of multiple constituents.[3] More important, based on our results, BSGRH not only has cytotoxic effects on cultured cancer cells,[5] a xenograft mouse pancreatic cancer model,[7] and a human skin cancer case,[29] but may also activate host immune system to fight against cancers.[29] More detailed studies will address mechanistic actions of BSGRH against cancers.

Modern chemical and biomedical techniques must be incorporated to study plant-based extracts that are intended for therapeutic purposes. For example, analytical chemistry techniques such as gas chromatography-mass spectrometry, tandem liquid chromatography-mass spectrometry, and high-performance liquid chromatography are appropriate for detailed analysis of chemical constituents and pharmacokinetics of BSGRH.[9] Molecular and cell biology techniques are useful in experimental models and clinical specimens to understand mechanisms of action.[6,7] Technologies and bioinformatics developed in the post–genomic era are very useful to understand pharmacodynamics and pharmacogenomics.[8] In addition, systemic clinical studies are required to demonstrate safety and efficacy of any plant-based therapeutic agent.

Chemical constituents of BSGRH differ significantly due to species of *Boswellia* plants as well as climates, geographical areas, time of harvest, and storage conditions of gum resins.[30] Methods of hydrodistillation can also yield different chemical profiles that can result in variations in biological activity.[6] It is, therefore, more difficult to standardize botanical extracts to meet pharmaceutical standards for therapeutic purposes. In addition to good laboratory practice and good manufacturing practice, the US Food and Drug Administration Guidance for Industry-Botanical Drug Products outlines good agricultural and collection practice for planting trees, harvesting and storage conditions, as well as processing procedures to obtain consistent therapeutic products and reliable clinical outcomes (http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm090946.htm). In order to meet modern medical standards and Food and Drug Administration guidelines for botanical drug development, identification of key compounds, mechanisms of action, phamacokinetics of key compounds, as well as efficacy and possible adverse effects will be addressed for future investigational new drug application.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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