Pharmacogn. Mag.
A multifaceted peer reviewed journal in the field of Pharmacognosy and Natural Products
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ORIGINAL ARTICLE

Effect of Aging and Geographical Variations in the Content of Guggulsterones and Metabolomic Profiling of Oleogum Resins of *Commiphora wightii*: The Indian Bdellium

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Submitted: 16-Feb-2021 Revised: 27-Jul-2021 Accepted: 09-Sep-2021 Published: 24-Jan-2022

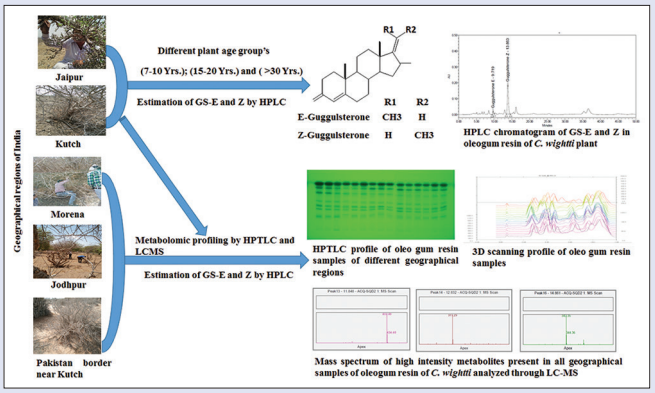
ABSTRACT

Background: The oleo-gum resin of *Commiphora wightii* has been utilized for centuries in Ayurvedic medicine for the treatment of various diseases. Ruthless exploitation of this species with negligible conservation efforts has led to its inclusion in the International Union for Conservation of Nature assemblage of endangered plant species. **Objectives:** In this paper, the impact of plant aging and geographical variations of guggulsterone (GS) content in oleo-gum resin collected from different geographical regions of India has been examined. **Materials and Methods:** The oleo-gum resin samples of different age groups and geographical regions of India (Kutch, Morena, Jodhpur, Jaipur, and Pakistan border of Kutch) were collected directly from the site and examined to check the concentration of GS-E and Z by high-performance liquid chromatography. Comprehensive metabolomic profiling of samples was done through liquid chromatography–mass spectrometry. **Results:** The data showed that there is no significant variation was found in the concentration of GS-E and Z with the change in the age of *C. wightti* plant. The oleo-gum resin samples of Morena showed a high percentage range of GSs (0.88%–2.17% w/w), whereas Jaipur samples showed a lower percentage of GSs (0.56%–0.89% w/w). From metabolomics profiling, 11 high-intensity metabolites were identified in samples of all major regions of India. **Conclusion:** This study indicates that there is no impact of plant aging on the GS contents. The Indian regions such as Morena, Kutch, and Pakistan border near Kutch regions can be used as a potential source for mass multiplication of guggul plants to get the good quality of the oleo-gum resin.

Key words: *Commiphora wightii*, metabolomic profiling, oleo-gum resin, plant aging

SUMMARY

- Comprehensive metabolomic profiling of oleo-gum resin samples of different geographical regions of India has been done to evaluate the impact of plant aging and geographical regions on the concentration of guggulsterone (GS) E and Z. No significant variation on the concentration of GSs was observed with the increase in plant age of *Commiphora wightti*. The oleo-gum resin samples collected from Morena regions showed the highest concentration of GSs followed by Kutch and Pakistan border regions near Kutch. Hence, these Indian regions can be evaluated as a potential source for mass multiplication of guggul plants to get a good quality of the oleo-gum resin.



Abbreviations: GS: Guggulsterone; RT: Retention time; LC-MS: Liquid chromatography–mass spectrometry; HPLC: High-performance liquid chromatography; HPTLC: High-performance thin-layer chromatography; DPPH: α, α-diphenyl-β-picrylhydrazyl.

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DOI: 10.4103/pm.pm_76_21

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INTRODUCTION

Commiphora wightii (Arn.) Bhandari is a gum bearing (Greek word *kommi* means "gum" and *pheros* means "to bear") medicinal important plant species which grows in arid, rocky, and semi-arid regions of India, Pakistan, Arabia, China, Tropical and Northern Africa, and other countries.[1,2] In the Indian subcontinent, it is mainly found in arid and rocky tracts of Madhya Pradesh, Karnataka, Andhra Pradesh, and Thar desert region of Rajasthan, Gujarat,[3] Balochistan (Pakistan), and Sindh (Pakistan).[4] The oleo-gum resin exudates from *Commiphora mukul* are used for various medicinal preparations and are commonly known as guggul or Indian bdellium. This gum resin, called guggulipid, is present in the ducts of C. wightti plant.[5] The commercial tapping, done to meet the high demand of oleo-gum resin in both national and international markets, affects its growth rate[6] and may also cause premature death of the tree by making

Cite this article as: Verma RK, Ibrahim M, Fursule A, Mitra R, Sastry JL, Ahmad S. Effect of aging and geographical variations in the content of guggulsterones and metabolomic profiling of oleogum resins of *Commiphora wightii*: The Indian bdellium. Phcog Mag 2021;17:774-9.

it susceptible to fungus and insect infection.[7] The excessive collection of gum resin can be destructive to the plant as it causes carbohydrates to be spent on exudates and may weaken the tree, which, in turn, slows down its growth and reproduction.[8,9] Tapping of trees causes small trees to suffer more than large trees, as they have lesser available stored carbohydrates. Conversely, the high carbon budget of large-sized trees yields more resins.[8,9] While no scientific data has been evaluated till date to study the impact of plant age on the percentage of GS-E and GS-Z. Hence, the present study was designed to evaluate the percentage of GS-E and GS-Z in different age group samples of oleo-gum resin of *C. wightti* collected from Kutch (Gujarat) and Jaipur (Rajasthan) regions of India.

Furthermore, ruthless exploitation of this species has led to a continuous decline in its population. It has been categorized as "Data Deficient in the assemblage of International Union for Conservation of Nature in 2008" due to lack of research in the establishment of its conservation status. The Indian government has covered it under the rare, endangered, and threatened category.[6] In the current scenario, hardly a few wild populations of *C. wightti* were found in Rajasthan and Gujarat.[10] Recently, the Government of India has also banned the export of gum resin considering the overexploitation of this plant as it has a very high market price in international trade.[11] Hence, mass cultivation of guggul plants in various major regions of India is necessary to procure this valuable medicinal plant. For this, the major geographical regions of India need to be evaluated. However, very limited studies based on the seasonal and geographical variations in GS content in oleo-gum resin have been examined to determine the optimum collection time and to identify suitable locations for large-scale cultivation of *C. wightii*. The available studies are limited to a specific region of India.[12] Although comprehensive metabolic profiling of leaves, stem, fruits, and gum resin samples has been reported to reveal the seasonal differences, distinct chemotypes of *C. wightti,*[13-15] and geographical variation study was done by Kulhari *et al*., 2013 in stem part of *C. wightti* of Rajasthan, Gujarat, and Haryana regions,[16] no comprehensive study has been done till date to evaluate the quality of oleo-gum resin in the major regions of India such as Gujarat, Rajasthan, Madhya Pradesh, and Pakistan border area near Kutch (Gujarat). Keeping in mind the endangered status and medicinal importance of *C. wightii,* the present study was designed to evaluate the various major geographical regions of India such as Kutch (Gujarat), Morena (Madhya Pradesh), Pakistan border near Kutch region of Gujarat, Jaipur, and Jodhpur (Rajasthan) based on the GS's content and metabolomics profiling through liquid chromatography–mass spectrometry (LC-MS) to study the geographical behavior of diverse metabolites present in the *C. wightti*. Metabolite profiling provides information about a plethora of metabolites and thus is an efficient tool to screen plants for novel bioactive compounds from Phyto resources. Metabolomics is the most suitable tool to assist in the understanding of such responses.[17] In the present study, metabolomics has been employed not only for comprehensive metabolic profiling to get the geographical diversity of metabolites but also to identify the high-intensity metabolites present in different geographical regions of India to explore the concept of phytotherapeutic agents.

MATERIALS AND METHODS

Materials

The chemical and solvents used for the extraction and chromatography were procured from Thermo Fisher Scientific India Pvt. Ltd., India. The reference standards of GS E and Z were purchased from Natural Remedies Pvt. Ltd., Bangalore, India.

With the help of local peoples, different age group samples of oleo-gum resins were directly collected from the sites of Kutch and Jaipur regions who were engaged in the production and cultivation of guggul plants for more than 40 years by traditional tapping method. Other samples (15–20 year old plants) of different geographical regions were also collected directly from the regions of Morena (Madhya Pradesh), Kutch (Gujarat), Kukus (Jaipur, Rajasthan), near the Pakistan border of Kutch (Dayapur and Gadholi), and Jodhpur (Rajasthan). The authenticity of all samples was kindly checked by Dr. Avi Fursule, Bioresource Department, Dabur Research and Development Center, Dabur India Limited, Sahibabad (U. P), India. The samples were collected (two replicates of each plant age group and three replicates of all different geographical regions) from December 2018 to February 2019. Specimens of all samples are preserved at the Bioresource Department, Dabur Research and Development center, Dabur India Limited, Sahibabad (U. P), India.

Extraction of metabolites

The oleo-gum resins (1 g each) were extracted with 100 mL acetonitrile by refluxing for 1 h on the water bath. The solvent portions were filtered and make up the volume up to 100 mL with acetonitrile.[18]

Quantification of guggulsterone-E and Z by high-performance liquid chromatography

GS contents were identified as well as quantified by using high-performance liquid chromatography (HPLC), methodology as mentioned in Indian Pharmacopeia, 2018.[18] Chromatography was performed using isocratic elution of acetonitrile–water 45:55 (v/v) with a flow rate of 2.0 mL min^{-1}. The analyses were performed using a reversed-phase C_{18} column (4.6 mm × 250 mm, 5 µm). The detection of GS-E and Z was done at 244 nm (Waters, Alliance e2695) equipped with a PDA detector, vacuum degasser, and column oven. The resultant peaks of the compounds were identified by comparing the retention time (RT) of the standard compounds with that of different peaks obtained in the HPLC analysis of sample extracts.

High-performance thin-layer chromatography fingerprinting

The oleo-gum resin samples extracted in acetonitrile were analyzed for high-performance thin-layer chromatography fingerprinting. Precoated alumina thin-layer chromatography (TLC) silica gel $60F_{254}$ plate (20 cm × 10 cm with 0.2 mm thickness, Merck, Darmstadt Germany) was used for sample analysis. Samples were applied on TLC plate by semiautomatic sample applicator Linomat-V using a 100 µl Hamilton syringe. The application volume of 10 µl was used with a maintained application speed of 150 nL/s using 6.0 mm band length. The best separation was observed in the mobile phase ratio of chloroform: methanol (90:10, %v/v). The plate was transferred to a CAMAG twin trough glass tank with presaturated mobile phase for 15 min using Whatman no. filter paper no 1. The developed plate was developed up to 80 mm in linear ascending mode, air-dried, and scanned at 254 nm and 366 nm using D_2 and Hg lamps, respectively. TLC scanner III (CAMAG, Switzerland) was used with a slit dimension of 4.0 mm × 0.30 mm, and the scanning speed was 10 mm/s. Further, the developed plate was dipped into 0.05% methanolic α, α-diphenyl-β-picrylhydrazyl (DPPH) reagent for 10 s. The plate was then covered with aluminum foil and kept in a dark condition for 15 min for the incubation to visualize the spots in visible light.

Liquid chromatography–mass spectrometry analysis of metabolites

The samples prepared in acetonitrile were used for the analysis to identify the diversity of metabolites present in oleo-gum resins of different geographic regions of India. The chromatographic profiling

was performed on Alliance 2695 separation module interfaced with an Acquity SQD2 MS system (Waters Corp., Milford, MA) equipped with an ESI ion source. The metabolites were separated using a C18 column (BDS, 5 µm, 130 Å, 250 mm × 4.6 mm, Hyperclone; Phenomenex Inc., Torrance, CA) with a mobile phase consisting of acetonitrile 0.1% and formic acid in water 45:55 (v/v) with a flow rate of 1.0 mL min^{-1}. ESI interface with 90% splitting of the column flow was used for the mass detection of separated metabolites. Empower 3 software incorporated with the instrument was used to process the chromatographic and mass spectrometric data. The source temperature of MS detector and desolvation temparature were set at 150°C and 400°C, respectively. The capillary voltage and cone voltage were set to 3.2 kV and 30 V, respectively. The desolvation gas (N2) and cone gas (N2) were set to 950 L/h and 100 L/h, respectively. The acquisition of mass was done in total ion mode (TIC, 100–1,000 *m/z*) with a scan time of 3 s.

RESULTS

Estimation of guggulsterone-E and Z by high-performance liquid chromatography

The GS-E and Z content varied significantly in all different age group samples of oleo-gum resin samples of Kutch and Jaipur regions, although no specific trend in the percentage of GS-E and Z was observed with the age of plants. Even two samples of the Kutch region of the same age group and location (7–10 years) showed lots of variation in GS's content, whereas no such major difference was observed in all age group samples of Jaipur regions [Figure 1].

HPLC analyses of guggul gum collected from 15 mature plants of *C. wightii* growing naturally at different geographical regions of India showed remarkable variation in GS content without any interference at 242 nm. The concentration of GS-E and Z was found highest in Morena (2.17% w/w) and Kutch (1.67% w/w). The least concentration of GS was found in Jaipur (0.59% w/w). The optimum concentration of GS-E and Z was observed in both region samples of the Jodhpur and Pakistan border near the Kutch region (Dayapur and Gadholi), as shown in Figure 2.

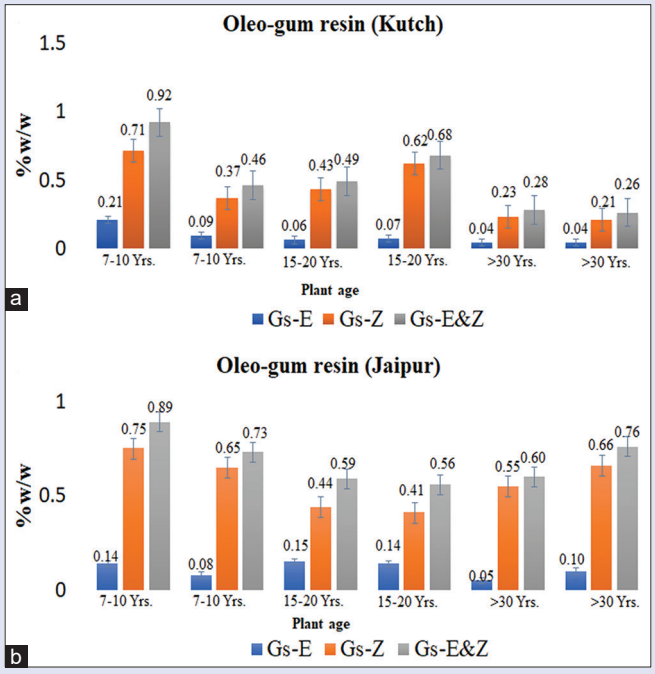

Figure 1: Concentration of the guggulsterone-E and Z in different plant age group samples of Kutch (a) and Jaipur (b) regions

Comparative high-performance thin-layer chromatography fingerprinting analysis of oleo-gum resins from different geographical regions of India

For TLC fingerprinting, oleo-gum resin samples were prepared in acetonitrile. Various mobile phases with different ratios were tried to get the well-resolved spots. Maximum separation of metabolites spots was obtained using solvent system chloroform: methanol (9:1, v/v). A total of 8 spots were obtained after scanning at 254 nm and 366 nm in samples of all geographical regions. After derivatization with 0.05% DPPH solution, bright yellowish spots were observed on the developed plate that indicate the presence of potent antioxidant compounds in oleo-gum resin samples of *C. wightti* plant [Figure 3]. TLC chromatograms and three-dimensional scanning profiles at 254 nm and 366 nm showed almost the same patterns for all samples.

Comparative metabolomics profiling by liquid chromatography–mass spectrometry

Analysis of ole-gum resin of *C. wightti* was analyzed and separation of metabolites was carried out by using LC-MS technique (C_{18} column, BDS, 5 µm, 130 Å, 250 mm × 4.6 mm, Hyperclone; Phenomenex Inc.). The study showed a significant metabolic difference among the different geographical regions. The oleo-gum resin samples of Jaipur, Kutch, and Morena regions showed a high number of metabolites, i.e., 307, 278, and 220, respectively, while Jodhpur and Pakistan border near Kutch regions showed the least number of metabolites (169 and 172, respectively).

The number of similar metabolites based on the *m/z* values at different RTs was analyzed and compared with each other for the number of similar moieties present in oleo-gum resin samples of different geographical regions of India [Figure 4].

Among the diversity of metabolites present in oleo-gum resin samples of different geographical regions of India, a total of 11 high-intensity metabolites were analyzed and tentatively identified based on the *m/z* value and literature survey. The study showed that these 11 metabolites were found to be present in all the geographical regions samples with high intensity. Table 1 summarizes all these comprehensive 11 metabolites present in all the oleo-gum resin samples of *C. wightti*.

DISCUSSION

C. wightii is one of the important medicinally plants, especially as a source of GS. This plant faces a high risk of endangerment due to various factors such as slow unsustainable growth, poor seed setting and lack of cultivation, germination rate, over-exploitation, excessive and unscientific tapping method, and invasion of alien species. In the present study, efforts have been made to evaluate the impact of plant age on the concentration of GSs. Kutch samples of the same age groups (7–10 years) showed a wide variation in GS's content (0.92 and 0.46% w/w), whereas samples from Gujarat of the same age group did not show any significant difference in GS's content (0.89 and 0.73% w/w). In the case of Kutch samples, the concentration of GSs was found very less (0.26% and 0.28% w/w) in plants with an age group of more than 30 years, while the Gujarat samples showed little variation in GS's concentration as compared to the early age group samples. Overall, no specific trend in the percentage of GS-E and Z was observed with the age of plants. There are some other factors that impact the production of GS in intact plants, as the production of oleo-gum resin is a stress-induced phenomenon. Factors such as individual plant performance (morphotypes and genotypes),

Table 1: List of high-intensity metabolites identified in oleo-gum resin samples of *Commiphora wightti* collected from different geographical regions of India

R_t (min)	*m/z*	Tentatively identified compounds			
		Name	Molecular formula	Class of compound	Reference
10.4	340.32	Dehydroguggulsterone-M	$C_{22}H_{28}O_3$	Steroid	[19]
11.84	432.48	Guggulsterol-I	$C_{27}H_{44}O_4$	Sterol	[20]
12.83	310.29	pregna-1,4-diene-3,16-dione	$C_{21}H_{26}O_2$	Steroid	[21]
14.85	342.35	guggulsterone-M	$C_{22}H_{30}O_3$	Steroid	[19]
21.34	312.32	Guggulsterone E	$C_{21}H_{28}O_2$	Steroid	[22]
24.93	428.47	stigmasta-5,22-diene-3,11-diol	$C_{29}H_{48}O_2$	Stigmastane-type steroid	[23]
27.15	314.32	20-hydroxy-pregna-4,6-diene-3-one	$C_{21}H_{30}O_2$	Ketosteroid	[21]
29.03	312.32	Guggulsterone-Z	$C_{21}H_{28}O_2$	Steroid	[20]
34.04	314.32	mansumbinone	$C_{22}H_{34}O$	Triterpenoid	[24]
53.12	412.42	Stigmasterol	$C_{29}H_{48}O$	Stigmastane-type steroid	[25]
75.8	414.49	beta-Sitosterol	$C_{29}H_{50}O$	Sterol	[26]

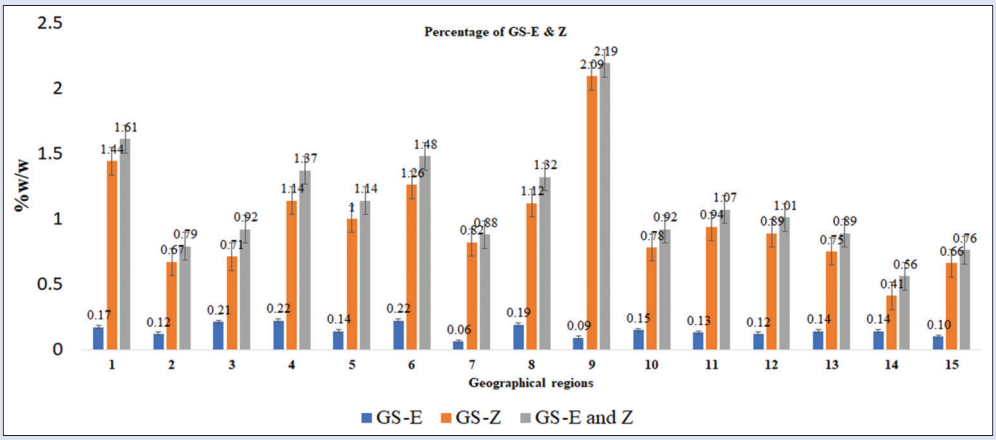

Figure 2: Concentration of the guggulsterone-E and Z in oleo-gum resin samples of Kutch (1,2,3), Pakistan border near Kutch region (4,5,6), Morena (7,8,9), Jodhpur (10,11,12), and Jaipur (13,14,15)

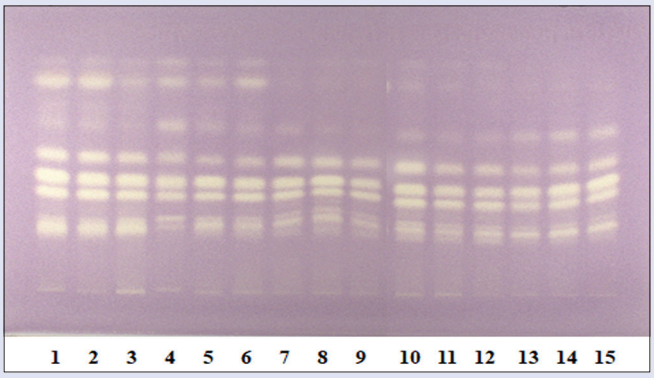

Figure 3: Thin-layer chromatography fingerprinting profile of oleo-gum resin samples of Kutch (1, 2, 3), Pakistan border near Kutch (4,5,6), Morena (7,8,9), Jaipur (10,11,12), and Jodhpur (13, 14, 15) at visible light after spraying with 0.05% methanolic solution of α, α-diphenyl-β-picrylhydrazyl

ecological (geographical and seasonal), cultivation practices, pathogens and elicitors (methyl jasmonate, ethrel, and salicylic acid) as well as tapping methods significantly affect the production of secondary metabolite GS in intact plants.[27,28] Hence, the present investigation reports that there is no specific impact of plant ages on the percentage yield of GSs.

A comprehensive geographical study of major regions of India showed remarkable variation in GS contents. The highest concentration of total GS-E and Z was found in the Morena region (2.19% w/w), whereas the lowest concentration was observed in the Jaipur region (0.56% w/w). Second, the highest concentration was found in Kutch samples (1.61% w/w). The samples collected from the Pakistan border of Kutch regions showed a good percentage of GSs content (1.14%–1.48%w/w) in all the samples. The samples from the Jodhpur regions also showed an optimum concentration range of GSs (0.92%–1.07% w/w). Identification of the Indian regions producing a higher concentration of GS may play an important role in designing mass cultivation as well as conservation strategies. The present study indicates that Indian regions such as Morena, Kutch, Jodhpur, and Pakistan border near Kutch regions might be used as a potential source for mass multiplication of guggul plants to get good quality of the oleo-gum resin. Quality control analyses of herbal products are one of the major concerns for manufacturing industries. TLC fingerprinting is commonly used to standardize the raw material or its extracts by developing its unique metabolite pattern so that the quality of the used extract can be checked for its further use. In this context, we have developed the TLC method to explore the oleo-gum resin of different geographical regions. All samples of different regions showed the same fingerprint profile, which indicates the presence of similar types of metabolites patterns. Moreover, LC-MS analysis was done to identify the metabolic differentiation present in the oleo-gum resins. Comparative metabolomics profiling by LC-MS reveals the percentage similarity of the diversity of metabolites present in different geographical regions of India. In the present study, an effort has been made to check that how much similar *m/z* values were found among all the region samples. The oleo-gum resins samples of the Jaipur and Kutch regions showed a high

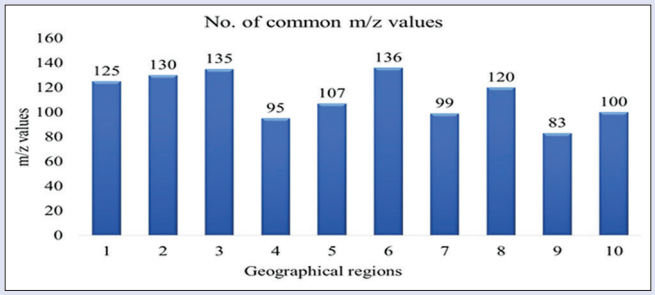

Figure 4: Comparatively common ions present in Kutch vs Morena (1), Kutch vs Pakistan border of Kutch (2), Kutch vs Jaipur (3), Kutch vs Jodhpur (4), Morena vs Pakistan border of Kutch (5), Morena vs Jaipur (6), Morena vs Jodhpur (7), Pakistan border of Kutch vs Jaipur 8), Pakistan border of Kutch vs Jodhpur (9) and Jaipur vs Jodhpur (10) regions of India

number of metabolites based on *m/z* values (307 and 278, respectively) as compared to other regions. While comparing the metabolites of all the oleo-gum resin samples, the Kutch and Jaipur samples had the maximum similar ions (>120 *m/z* values) with most of the samples of different geographical regions. On the other hand, Jodhpur region samples showed the least number of similar *m/z* values with all regions. Chromatographic-based metabolomics is a powerful approach for the chemical and pharmacological standardization of plant extract and it has the potential in the field of natural product research to develop herbal-based medicine.[29] In the present study, other than GS-E and Z which are commonly used as marker compounds, nine high-intensity significant metabolites consisting of dehydro GS-M, guggulsterol-I, pregna-1,4-diene-3,16-dione, GS-M, stigmasta-5,22-diene-3,11-diol, 20-hydroxy-pregna-4,6-diene-3-one, mansumbinone, stigmasterol, and β-sitosterol have been tentatively identified in the oleo-gum resin samples of different geographical regions of India. The intensity of these metabolites was found high in all regions. These identified metabolites have several therapeutic properties such as hypoglycemic, hypolipidemic, antioxidant, carcinogenic, cardiovascular disease, anti-inflammatory, and antimicrobial.[30] Hence, these high-intensity metabolites can be explored as a valuable natural resource for the evidence-based development of new nutraceuticals and phytotherapeutics.

CONCLUSION

This study indicates that there is no impact of plant aging on the GS contents. The Indian regions such as Morena, Kutch, and Pakistan border near Kutch regions can be used as a potential source for mass multiplication of guggul plants to get good quality oleogum resin. Comparative metabolomics profiling by LC-MS reveals the percentage similarity of the diversity of metabolites present in different geographical regions of India. From the present study, a total of 11 high-intensity metabolites were identified which can be explored as valuable natural resources for the evidence-based development of new nutraceuticals and phytotherapeutics.

Acknowledgements

The authors are thankful to BNPL, SPER, JH, and Dabur India Limited, for their help and laboratory supports.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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